COLUMBIA LIBRARIES OFFSITE
HEALTH SCIENCES STANDARD
HX00048658
RECAP

RC41 St3
Columbia University
in the City of New York 13
College of Physicians and Surgeons

Library

From the Library of
Bruno Hood M.D.
P & S/85

TWENTIETH CENTURY

PRACTICE

AN INTERNATIONAL ENCYCLOPEDIA

OF

MODERN MEDICAL SCIENCE

BY

LEADING AUTHORITIES OF EUROPE AND AMERICA

EDITED BY

THOMAS L. STEDMAN, M.D.

NEW YORK CITY

IN TWENTY VOLUMES

VOLUME XIII

INFECTIOUS DISEASES

NEW YORK

WILLIAM WOOD AND COMPANY

1898

Copyright, 1898,
By WILLIAM WOOD & COMPANY

RC41
St3
v.13

PRESS OF
THE PUBLISHERS' PRINTING COMPANY
32-34 LAFAYETTE PLACE
NEW YORK

CONTENTS.

PAGE

PTOMAÏNS, TOXINS, AND LEUCOMAÏNS, ... 1
Bacterial Poisons, ... 3
Ptomaïns, ... 9
Bacterial Proteids, ... 21
Bacterial Toxins, ... 23
Food Poisoning, ... 26
Mussel Poisoning, ... 27
Fish Poisoning, ... 33
Meat Poisoning, ... 42
Milk Poisoning, ... 49
Cheese Poisoning, ... 57
Vegetable Food Poisoning, ... 66
Poisons of the Specific Infectious Diseases, ... 80
Leucomaïns, ... 110
Relation of Leucomaïns to Disease, ... 128
INFECTION AND IMMUNITY, ... 133
Infection, ... 135
Chemotaxis, ... 165
Predisposition to Infectious Diseases, ... 166
Insects as Carriers of Infection, ... 187
Mixed Infection, ... 190
Late Results of Infection, ... 193
External Predisposing Influences, ... 196
Rôle of the Nervous System, ... 200
Periods of Incubation and Infectiousness, ... 203
Prevention of Infectious Diseases, ... 204
Immunity, ... 205
Destruction of Immunity, ... 208
Theories of Immunity, ... 209
Serum Treatment, ... 235
General Properties of Serum, ... 235
Serum Treatment in Experimental Diseases, ... 240
Serum Treatment in Human Diseases, ... 248
Serum Treatment in Poisoning by the Vegetable Toxalbumins and the Venoms of Serpents, ... 265
Characteristics of the Immunity due to Serum, ... 268
The Active Element of the Serum, ... 270
Theory of the Protective Action of Serum, ... 273
Nature of the Germicidal Constituent of the Blood Serum, . . . 277
The Hereditary Transmission of Immunity, ... 279
WATER-BORNE DISEASES, ... 281
Introduction, ... 283

PAGE

Diseases Caused by Non-Living Matter, ... 283
Plumbism, ... 283
Poisoning by Zinc, Copper, or Arsenic, ... 287
Dyspepsia, Diarrhœa, and Ptomaïn Poisoning, ... 287
Diseases Caused by Living Organisms, ... 289
The Entozoa, ... 290
Bacteria, ... 293
Typhoid Fever, ... 302
Cholera, ... 324
Malaria, ... 351
Dysentery, Diarrhœa, and Yellow Fever, ... 357
Preventive Measures, ... 359
Conclusions, ... 363
Bibliography, ... 364
The Duration of the Periods of Incubation and Infectiousness in Acute Specific Diseases, ... 365
Smallpox, ... 373
Chickenpox, ... 374
Measles, ... 374
German Measles, ... 375
Scarlet Fever, ... 376
Diphtheria, ... 377
Whooping-cough, ... 378
Mumps, ... 379
Typhus Fever, ... 380
Typhoid Fever, ... 381
Relapsing Fever, ... 382
Dengue, ... 382
Influenza, ... 382
Yellow Fever, ... 383
Asiatic Cholera, ... 384
Bubonic Plague, ... 384
Malarial Fever, ... 385
Bibliographical References, ... 385
Smallpox, ... 387
Definition, ... 389
History, ... 390
Etiology, ... 394
Clinical History and Symptomatology, ... 408
Complications and Sequelæ, ... 430
Pathology, ... 441
Diagnosis, ... 445
Prognosis, ... 452
Treatment, ... 457
Bibliographical References, ... 496
Vaccina, ... 499
Discovery of Vaccination, ... 501
The Relations of Cowpox, Horsepox, and Vaccina in Man, . . . 503
The Non-Identity of Variola and Vaccina, ... 508
The Active Elements of Vaccine Virus, ... 512

PAGE
The Normal Vaccinal Eruption, ... 515
Vaccinal Receptivity, ... 518
Vaccinal Immunity, ... 518
Anomalies of the Vaccine Eruption, ... 527
Coincident Eruptions, ... 532
Secondary Infections, ... 533
Animal Vaccine, ... 545
Indications and Contraindications of Vaccination, ... 549
Methods of Vaccination, ... 550
Bibliographical References, ... 551
MUMPS, ... 553
History, ... 555
Geographical Distribution and Epidemics, ... 556
Pathological Anatomy, ... 558
Bacteriology, ... 559
Etiology, ... 563
Symptoms, ... 568
Course and Duration, ... 577
Extrasalivary Localizations and Complications, ... 578
Prognosis, ... 598
Diagnosis, ... 595
Treatment, ... 598
Bibliographical References, ... 602
INDEX, ... 605

Digitized by the Internet Archive
in 2010 with funding from
Open Knowledge Commons

http://www.archive.org/details/twentiethcentury13sted

CONTRIBUTORS TO VOLUME XIII.

P. Brouardel, M.D., Paris.

Professor of Medical Jurisprudence and Dean of the Faculty of Medicine at the University of Paris; Physician to the Hôpital de la Charité.

Jules Comby, M.D., Paris.

Physician-in-chief to the Hôpital des Enfants; Honorary Physician to the Dispensaries for Sick Children of the Société Philanthropique; Editor of Archives de Médecine des Enfants.

Harold C. Ernst, M.D., Boston.

Professor of Bacteriology, Harvard Medical School.

Ernest Hart, D.C.L., M.R.C.S., London.

Chairman National Health Society; Editor of the British Medical Journal.

John William Moore, M.D., M.Ch., F.R.C.P.I., Dublin.

Senior Physician to, and Lecturer on, Clinical Medicine at the Meath Hospital; Consulting Physician to the Cork Street Fever Hospital, to the Coombe Lying-in Hospital, and to the Drumcondra Medical and Surgical Hospital; Joint Professor of the Practice of Medicine in the Schools of Surgery of the Royal College of Surgeons in Ireland; Editor of the Dublin Journal of Medical Science.

Solomon C. Smith, M.D., M.R.C.P., M.R.C.S., London.

Consulting Medical Officer, Royal Halifax Infirmary; Physician to the Westminster General Dispensary; Editor of The Hospital.

Victor C. Vaughan, M.D., Ph.D., Ann Arbor.

Dean and Professor of Hygiene and Physiological Chemistry, University of Michigan.

Dawson Williams, M.D., F.R.C.P., London.

Physician to the East London Hospital for Children.

PTOMAÏNS, TOXINS, AND LEUCOMAÏNS.

BY

VICTOR C. VAUGHAN,

ANN ARBOR, MICH.

VOL. XIII.—1

PTOMAÏNS, TOXINS, AND LEUCOMAÏNS.

BACTERIAL POISONS.

That the infectious diseases are caused by certain microorganisms has been positively demonstrated. For hundreds of years the logical minds of the profession saw that the theory of a contagium vivum was the only rational explanation of the spread of epidemics, but the medical world was compelled to await the discovery and development of the compound microscope before the causal relationship of minute forms of life to diseases could be demonstrated to the senses. The early observations of Davaine and Pollender, made about the middle of the nineteenth century, followed, as they were, by the laborious and fruitful researches of Pasteur, Koch, and others, have lifted our knowledge of the etiology of the infectious diseases from the uncertain sands of speculation and placed it upon the solid rocks of science. No one will claim that the labors of the century just closing leave no undiscovered facts in this field for the future investigator, but he can proceed, thanks to these labors, upon lines as truly scientific as those that guide the researches of the chemist and the physicist.

It is true that in these the last years of the nineteenth century there are a few who still question the causal relationship of germs to disease, but professionally these live in a past now so remote that we may consider them as only of archeological interest. We will therefore start with the demonstrated fact that the infectious diseases are caused by microorganisms, and upon this as a basis we will study the relation of the bacterial products to disease.

Granting that certain bacteria do by their growth within the animal organism disturb the normal functions of the cells of this organism, we are ready to inquire into the agencies by which these disturbances are induced. How do bacteria cause disease? In what way does the specific bacillus of diphtheria induce the symptoms of this disease and cause death? These questions arose soon after it had been demonstrated that microorganisms constitute the essential factor in the causation of the infectious diseases. Since the bacillus

of anthrax was one of the first of the pathogenic bacteria isolated, it became the basis of many of the theories offered in answer to the questions here propounded.

Bollinger suggested that the apoplectic form of anthrax might be due to the deprivation of the oxyhæmoglobin of the blood of its oxygen by the bacilli. This theory was rendered plausible by the fact that the bacilli of anthrax are aërobic and the symptoms resemble those of asphyxiation. The most important of these symptoms are subnormal temperature, dyspnœa, cyanosis, dilated pupils, and convulsions. Furthermore, the post-mortem findings are in accord in the main with this theory. The veins are filled with dark blood, the parenchymatous organs are cyanotic, and the lungs are engorged. The rapid course of the disease was also pointed out as showing the resemblance of this form of anthrax to poisoning with hydrocyanic acid, which was then believed to act as a poison by depriving the blood of its oxygen. The estimate of Davaine, which placed the number of bacilli in each drop of blood of an animal dying with anthrax at from eight to ten millions, made it easy to understand how the rapid withdrawal of oxygen from the corpuscles might be accomplished. Pasteur at one time was inclined to support this theory, and he advanced the additional argument that birds were not susceptible to this disease, and he accounted for their insusceptibility by supposing that the blood corpuscles of these animals do not part with their oxygen readily. This theory was soon shown to be wholly untenable. More extended researches demonstrated that the number of bacilli in the blood had been greatly overestimated, and that in many instances death resulted when the number of germs present in the blood was small. Joffroy showed experimentally that death might occur before any bacilli reached the blood. Oemler and Feser ascertained that insusceptibility to anthrax was not common to all birds, and indeed that some species are highly susceptible. Spectroscopic studies of the blood showed that even when filled with anthrax bacilli, its oxyhæmoglobin is not appreciably diminished. It was observed that difficult respiration is not a constant accompaniment of the disease, which must be the case in asphyxiation. When animals sick with anthrax were compelled to breathe air containing a large volume of oxygen, the symptoms were not modified, nor was death delayed. Nencki determined quantitatively the process of oxidation going on in the blood of anthrax animals by estimating the amount of phenol eliminated after the administration of weighed quantities of benzol and thus found that processes of oxidation were not retarded. Thus the deoxidation theory was found not to be true for anthrax, and if not true for anthrax, it certainly could not be true for

any other infectious disease. In many of these diseases the bacilli are not found in the blood at all. Indeed, in some, and among these are to be found such speedily fatal diseases as tetanus and diphtheria, the specific germ spreads over comparatively a small area around the point of infection. Again, some of the most virulent pathogenic bacteria are anaërobic, manifesting their maximum growth and virulence in the absence of oxygen. The deoxidation theory has been found to be wanting both when applied to anthrax in particular and to the infectious diseases in general.

A second theory may be designated as that of anæmia. It was suggested that the bacteria destroy the red corpuscles of the blood. This theory never had any scientific support. As has been stated, in many diseases the bacteria are not found in the blood, and the disintegration of the corpuscles cannot be confirmed by microscopical examination.

Thirdly, it was suggested that the bacteria might prove harmful by consuming to a marked extent the proteids of the organism and thus depriving the animal of its sustenance. It is a well-known fact that microorganisms grow abundantly in solutions of certain proteids and thus the cells of certain organs might be so impoverished that they could not normally perform their functions. That this theory is not satisfactory must be evident on the most superficial inquiry. In the first place, many of the infectious diseases destroy life so speedily that the fatal effects cannot be due to the consumption of any large proportion of the proteids of the body. In the second place, the location and limitation of the infecting microorganisms are often such that they come in contact with only a very small amount of the proteid tissue. Thirdly, the symptoms are not those of starvation. It is true that many of the infectious diseases are accompanied by marked marasmus, but this is due to faulty digestion or assimilation, or to hastened metabolism, as in those disorders which are accompanied by severe febrile manifestations; but even the fever is not due to the large consumption of proteid tissue by the bacteria.

The mechanical-interference theory is the one that has found its strongest support in the study of anthrax. If a section from a kidney or the liver of a guinea-pig dead from anthrax be properly stained and examined under the microscope, the bacilli will often be found to be present in such large numbers that they form emboli, which not only fill, but actually distend the capillaries and larger blood-vessels, and thus interfere with the normal functions of these organs. Similar conditions are sometimes observed in the spleen and lungs. From these appearances it was inferred that the bacilli

produce the diseased condition simply by accumulating in large numbers in these important organs and thus mechanically interrupting their functions. Toussaint thought that the symptoms and death in anthrax might be due to stoppage of the pulmonary circulation by the formation of emboli in the lungs. However, that this is a frequent occurrence has been shown not to be true by repeated post-mortem examinations. This theory never found support in any other disease than anthrax. However, I am inclined to think that if similar conditions had been found in the other infectious diseases, this would have long remained the dominant theory, and I am not ready to deny that mechanical interference can be entirely overlooked in anthrax any more than it can in diphtheria, in which there can be no doubt that death sometimes results from the filling of the larynx with false membrane. Moreover, the difficulty which the chemist has experienced in discovering any powerful poison in anthrax cultures would have given material aid to this theory had anthrax been the only disease studied or had similar conditions been found in the other bacterial diseases. However, the inapplicability of the theory of mechanical interference to tetanus, to most cases of diphtheria, to typhoid fever, to Asiatic cholera, and even to the septicæmias other than anthrax, is self-evident.

The vital deficiencies in the above-mentioned theories being so self-evident, the bacteriologist has been led to give his attention to the chemical products of bacterial activity, and in doing so he has undoubtedly found the true answer to the question, how do germs induce disease? The chemical theory of the action of bacteria admits of several possibilities, some of which will be briefly discussed.

1. The bacterium may elaborate a soluble chemical ferment, which by its action on the animal body causes the symptoms of the disease and induces death. That many bacteria do produce chemical ferments has been demonstrated. Both diastatic and peptic ferments have been obtained from cultures of certain bacteria, and it is not altogether improbable that the peptic ferment, at least, may play a part in breaking up the continuity of the tissues in which the bacteria grow. Bitter has shown that the bacillus of Asiatic cholera, when grown in beef-peptone cultures, produces a ferment which may remain active after the bacillus has been destroyed. This ferment may convert a large amount of coagulated albumin into peptones. It resembles pancreatin more than pepsin inasmuch as it is more active in alkaline than in acid solutions. This resemblance to pancreatin is further shown by the fact that its activity is increased by the presence of certain chemicals, such as sodium carbonate and sodium salicylate. Fermi has isolated this ferment in the following

manner: To gelatin, which has been liquefied by the cholera bacillus, sixty-five-per-cent. alcohol is added. This precipitates the proteids, but not the ferment. After twenty-four hours the insoluble proteid is removed by filtration, and the ferment is precipitated from the filtrate by the addition of absolute alcohol. This precipitated ferment may be dried, dissolved in an aqueous solution of thymol, and its peptonizing properties demonstrated on gelatin or coagulated albumin. Rietsch believes that the destructive changes observed in the intestines in cholera are due to the action of this peptonizing ferment. These and other experiments have shown that bacteria may produce soluble chemical ferments, and it will appear later that some of the specific toxins have certain resemblances to those imperfectly known bodies designated as chemical ferments.

2. The germ may, either by its direct action as a living ferment, or indirectly through a soluble chemical ferment secreted by itself, split up some of the complex proteid constituents of the organism into simpler bodies, among which there may be poisonous substances. The action, according to this theory, would be similar to that by which the yeast plant splits up the sugar molecules into carbonic-acid gas and alcohol. That some of the pathogenic bacteria have such a cleavage effect upon proteid molecules is demonstrated by the fact that their products vary with the constituents of the nutritive media in which they are grown. Brieger found that although the Eberth bacillus grows well in solutions of peptone, it does not in this medium elaborate any poisonous basic products; while from cultures of the same bacillus in beef-tea he obtained an active alkaloidal body. Fitz observed that while the bacillus butyricus produces butyric acid by its action on carbohydrates, in glycerin it forms propylic alcohol; and Morin has found amylic alcohol among the chemical products of this germ. Brown has ascertained that while the mycoderma aceti converts ethylic alcohol into acetic acid, it converts propylic alcohol into propionic acid, and is without effect upon methylic alcohol, primary isobutylic alcohol, and amylic alcohol. While the last-mentioned bacteria are not pathogenic, a study of their activities gives us reasonable assurance that at least some of the harmful products of the specific bacteria may originate in a similar manner. This theory of the cleavage action of bacteria does not necessitate the supposition that the poisonous substances have been an integral part of the bacterial cells. It assumes that the bacteria have an analytical action upon constituents of the animal tissue, splitting complex bodies into those of simpler structures.

3. The bacteria may convert their food into poisonous substances. This conversion of inert into poisonous material may occur

during the process of assimilation, *i.e.*, the content of the bacterial cell may be the active agent, or the conversion may occur during the process of elimination from the bacterial cell. That some of the pathogenic bacteria may act synthetically or constructively in the elaboration of their specific poisons has been demonstrated. Thus it has been shown that the bacilli of tetanus, diphtheria, and other diseases, when grown in media wholly free from proteids, will form proteid poisons. This can be accomplished only by a synthetical process. It is probable that the specific toxins are formed altogether in this way.

While bacteria may act diversely in the production of their specific poisons, there can no longer be any doubt that it is by virtue of their chemical products that they induce disease. The formation of chemical poisons is the only possible explanation of the symptoms induced by the bacilli of such diseases as tetanus and diphtheria, in which the germs are confined to relatively small areas and do not find their way into the circulation. Moreover, it has been positively demonstrated that the pathogenic bacteria do elaborate poisons and that animals treated with these chemical products manifest the symptoms of the disease, succumb to doses sufficiently large, and in some instances show the same lesions as those found in the animal dead from inoculation with the living germ. A further demonstration of the truth of these statements has been obtained by the actual detection of the chemical poison in the bodies of animals killed by inoculation with the bacteria. It was for a while argued by some that the formation of chemical poisons in the dead matter of meat-broth and other culture media by the germ does not prove that the same agent is capable of forming the same or similar products within the living body; but the isolation of tetanin by Brieger from the amputated arm of a man with tetanus supplied the first experimental answer to this criticism, and later other bacterial poisons have been obtained from the bodies of men and the lower animals. We now expect to find each specific pathogenic microorganism producing its characteristic poison or poisons.

Some years ago the writer formulated the following definition of an infectious disease, and recent investigations have confirmed its applicability:

An infectious disease arises when a specific pathogenic microorganism, having gained admission to the body, and having found the conditions favorable, grows and multiplies, and in so doing elaborates a chemical poison which induces its characteristic effects.

A study of the chemistry of bacteria has not only enabled us to understand how germs cause disease, but it has been of value in de-

termining the relation of certain bacteria to disease. The third and fourth of Koch's rules have in some cases been difficult of application, because the lower animals are often immune to many of the diseases to which man is susceptible. In all such cases the study of the effects of the chemical poisons of these bacteria on the lower animals may be of great service. A given bacterium may not multiply in the circulating blood nor in the living tissues of a dog, but failure to do this does not prove that the same germ might not cause disease in man; since every bacterium that causes disease does so by virtue of its chemical products, if these be isolated and injected into the dog in sufficient quantity a poisonous effect will most likely follow. This is not always true, because animals differ widely in their susceptibility to the chemical poisons, but a study of the action of the chemical products has been of great service. Thus a rat may eat largely of poisonous cheese without being injuriously affected, but if the harmful microorganism in the cheese be isolated, grown in pure culture, and its chemical poison obtained, the injection of a sufficiently large quantity of this into the animal will cause speedy death.

Again, the study of the chemistry of bacteria has shown us that there are many germs that do not grow at all upon living matter, but which may cause disease and death through the agency of chemical poisons formed in food before it is eaten or after it has been taken into the alimentary canal.

Classification of Bacterial Poisons.

It is quite impossible to classify satisfactorily the bacterial poisons at the present time; however, a provisional classification will be offered.

Ptomaïns.

Some of the chemical products of bacterial growth combine with certain mineral and vegetable acids, forming definite chemical salts, corresponding in this respect at least with the inorganic and organic bases. The members of this class are designated as ptomaïns, a name suggested by an Italian toxicologist, Selmi, and derived from the Greek word πτῶμα, meaning cadaver. The term ptomatin is preferred by Kobert on the ground that etymologically it is more correct. A ptomaïn may be defined as an organic chemical compound, basic in character and formed by the action of bacteria on nitrogenous matter. On account of their basic properties, in which they resemble the vegetable alkaloids, ptomaïns may be called putrefactive

or bacterial alkaloids. They have been called animal alkaloids, but this is a misnomer, because in the first place some of them are formed by the action of bacteria on vegetable proteids; and in the second place the term "animal alkaloid" is more strictly applicable to the leucomaïns, those basic bodies that result from tissue metabolism in the animal body. All ptomaïns contain nitrogen as an essential part of their basic nature. In this respect also they resemble the vegetable alkaloids. Some of them contain oxygen, while others do not. The former correspond to the fixed alkaloids, while the latter resemble the volatile alkaloids, nicotine and coniine. The kind of ptomaïn formed depends upon the germ producing it, the material on which it grows, and the conditions under which it grows—such as the temperature, the amount of oxygen present, and the stage of growth reached.

Poisonous action is not an essential property of ptomaïns. It is only necessary that the substance should be of bacterial origin and should be basic in its behavior towards acid, in order for it to be classed in this group. Indeed, many of the ptomaïns so far isolated are not, when administered in single doses at least, poisonous. Brieger has suggested that the term ptomaïn be restricted to the non-poisonous bacterial bases, and that the poisonous ones be denominated "toxins." Fortunately, this suggestion has not been adopted, and in the mean time the term toxin has come into use to designate quite a different class of bacterial products. Moreover, the poisonous effect of a given substance is largely a relative matter. While a single administration of a given substance, even in large quantity, may be followed by no visible or lasting effects, the continued production of the same substance in the body for days or weeks might be accompanied by most disastrous consequences.

The ptomaïns are not the most important or characteristic products of bacterial action. Indeed, the most recent researches in this department of etiology have demonstrated that the ptomaïn must be relegated to the class of less important bodies concerned in the production of the symptoms of disease. When it became known that some of the specific pathogenic germs elaborate, both in artificial cultures and in susceptible animals, poisonous basic substances, it was surmised that the symptoms of the diseases induced by the microorganism were due in all cases to such basic poisons, and many chemists labored diligently to isolate from cultures of each germ its special basic products. These labors, however, soon led to the conclusion that this assumption had been too hastily reached. It was found to be true that the symptoms of each and every infectious disease investigated are due to the chemical products of the

bacterium, but these chemical products are not generally basic in character, and consequently cannot be classed among the ptomaïns. Indeed, we do not know a specific infectious disease, the symptoms of which are due solely to ptomaïns. The most active poisons found among the bacterial products belong to another group, and this will be discussed later.

The following is a list of the ptomaïns reported up to the present writing, with a brief statement of the conditions under which they are formed and of their most important properties:

Methylamin, $CH_3.NH_2$.—Found in herring brine and in decomposing fish of various kinds. Brieger found this base in beef-broth cultures of the comma bacillus kept for six weeks at 37° to 38° C. Ehrenberg believed that he detected it in poisonous sausage, and obtained it from cultures of a bacillus found in the sausage. It is, however, non-poisonous, and is of chemical interest only. It is an easily inflammable gas, of strong ammoniacal odor, and is readily soluble in water.

Dimethylamin, $(CH_3)_2.NH$.—Found in putrefying gelatin and yeast. It has also been obtained from herring brine, decomposing fish, and poisonous sausage. It is non-poisonous, is a gas at ordinary temperature, but can be condensed to a liquid that boils at 8° to 9° C.

Trimethylamin, $(CH_3)_3N$.—Has been found in various kinds of decomposing vegetable and animal tissue. It may be quite abundantly present in herring brine. It is an interesting fact that trimethylamin has been obtained from ergot, but according to Brieger it does not exist preformed in this mould, but results from the splitting up of the cholin by the processes resorted to in extraction. It has been found in cultures of the comma bacillus, of streptococcus pyogenes, and of proteus vulgaris. The free base is a liquid at ordinary temperature, possessed of a penetrating fishy odor, and is poisonous only when administered in large quantities. The base boils at 9.3° C.

Ethylamin, $C_2H_5.NH_2$.—Ethylamin has been found in the distillation products of beet-sugar residues, in decomposing yeast, and wheat flour. It is an ammoniacal liquid, with a boiling-point of 18.7° C. It is not poisonous.

Diethylamin, $(C_2H_5)_2.NH_2$.—This base has been obtained from decomposing fish and poisonous sausage. It is an inflammable liquid, with a boiling-point of 57.5° C., and is devoid of poisonous properties.

Triethylamin, $(C_2H_5)_3N$.—Found in decomposing fish and poisonous sausage. It is a liquid, boiling at 89° C., slightly soluble in water, and non-poisonous.

Propylamin, $C_3H_7NH_2$. — There are two propylamins, CH_3-$CH_2CH_2.NH_2$ and $(CH_3)_2.CH.NH_2$. The former is the normal compound, is a liquid base, and boils at 48° C. The second is isopropylamin, and boils at 31.5° C. Propylamin has been obtained from mixed cultures of the bacteria of fæces. It is non-poisonous.

Butylamin, $C_4H_{11}N$.—Has been found in cod-liver oil. It is a colorless liquid, boiling at 86° C. It is diaphoretic and diuretic, and in large doses causes stupor and vomiting.

Isoamylamin, $(CH_3)_2.CH.CH_2.CH_2.NH_2$.—Found in decomposing yeast and in cod-liver oil. It is an alkaline liquid, possessed of a pleasant odor, and boiling at 98° C. It is an active poison, causing convulsions and death.

Caproylamin, $C_6H_{15}N$. — Hager obtained from putrid material what he thought to be a mixture of amylamin and caproylamin, and named it septicin. Caproylamin resembles amylamin in its action, but is less poisonous.

Tetanotoxin, $C_3H_{11}N$ (?).—Was found by Brieger and others in cultures of the tetanus bacillus. It causes tremor, paralysis, and convulsions.

Spasmotoxin.—The composition of this base has not been determined. It is found in cultures of the tetanus bacillus, and induces violent convulsions.

Dihydrolutidin, $C_7H_{11}N$.—This is an oily, caustic liquid, boiling at 199° C., and found in cod-liver oil. It is feebly poisonous, large doses causing depression, broken by periods of great excitement, and leading to paralysis of the posterior extremities and death.

Collidin (?), $C_8H_{11}N$.—This substance possesses the distinction of being the first ptomaïn obtained in a chemically pure condition. It was isolated by Nencki, in 1876, from decomposing pancreas and gelatin. It is isomeric, but not identical with aldehyde-collidin. It is a sirupy liquid, of nauseous, bitter taste.

Pyridin Base (?), $C_8H_{11}N$.—This is isomeric with collidin and the base just described. It was found in putrefying sea polyps, is a liquid, only slightly soluble in water, and boils at 202° C. There have been no exact studies concerning the action of this and the preceding base.

Hydrocollidin, $C_8H_{13}N$.—This base has been found in decomposing flesh from various sources. It is a colorless, oily liquid, with a penetrating odor like that of syringa. It boils at 205° C. This base is markedly poisonous. A dose of 1.7 mgm. was injected under the skin of a bird, and caused loss of coördination of movement, followed by paralysis and death. A quantity ten times as large caused vomiting, convulsions, paralysis, and death.

Parvolin, $C_9H_{13}N$.—This base has been found in decomposing mackerel and horse-flesh. Its identity with synthetical parvolin is probable, although not fully established. We possess no positive information concerning its action.

Unnamed Base, $C_{10}H_{15}N$.—Found in decomposing fibrin and jelly-fish. It is a brownish oil, possessing a feeble, unpleasant, coniine-like odor. In its action it resembles curare, but is less potent. It causes in frogs dilatation of the pupils, slowing of the respiration, and muscular paralysis.

Pyridin Base (?), $C_{10}H_{15}N$.—This substance has been obtained from sea polyps in an advanced stage of putrefaction. It forms a yellow, viscous liquid, with an odor resembling that of blooming broom. It boils at about 230° C., at which temperature it begins to decompose. It is only slightly soluble in water, and its physiological action has not been studied.

Unnamed Base, $C_{32}H_{31}N$.—This base forms a colorless, oily fluid, with a hawthorne-like odor. Its action is said to resemble that of veratrin.

Ethylidenediamin (?), $C_2H_8N_2$.—This base is probably not identical with ethylidenediamin. In mice and guinea-pigs it causes a free secretion from the mouth, nose, and eyes. The pupils are dilated and the eyeballs protrude. Dyspnœa comes on and death occurs after twenty-four hours. The heart is arrested in diastole.

Anthracin, $C_3H_6N_2$.—Obtained by Hoffa from pure cultures of the anthrax bacillus, in which, however, it exists in very small quantity. It causes at first increased respiration and action of the heart; then the respirations become deep, slow, and irregular; the temperature falls below the normal, the pupils are dilated, and a bloody diarrhœa sets in. On section the heart is found contracted, the blood is dark, and ecchymoses are observed in the pericardium and peritoneum. Hoffa claims to have found this poison in the bodies of animals dead of anthrax.

Trimethylenediamin (?), $C_3H_8N_2$.—Found by Brieger in cultures of the comma bacillus on beef-broth. It causes muscular tremor and violent convulsions.

Putrescin, $C_4H_{12}N_2$.—This diamin is a frequent product of bacterial activity and it has been found with cadaverin in the urine in cystinuria. It is a watery fluid, with a semen-like odor, and boils at 138° C. It is but feebly poisonous.

Cadaverin, $C_5H_{14}N_2$.—Found with putrescin as a frequent product of bacterial growth and in the urine in cystinuria. It has been suggested that the peculiar odor of cholera stools might be due to cadaverin, but Roos was not able to detect this base in the rice-water dis-

charges; however, he did find both putrescin and cadaverin in diarrhœal stools in which he also found a coliform bacillus. It is possible that the coniine-like body that has been so frequently observed in toxicological examinations may be cadaverin. It has been shown that both putrescin and cadaverin have a marked local effect, causing inflammation and necrosis. It is probable that the necrosis of the intestinal epithelial tissue in cholera may be due to the direct action of these bases. However, dogs fed upon very large quantities of cadaverin show no signs of intestinal irritation. It is also probable that the cystitis that invariably accompanies cystinuria may be due to the action of these bases upon the mucous membrane of the bladder. Cadaverin is one of the substances that may cause suppuration without bacteria.

Neuridin, $C_5H_{14}N_2$.—Neuridin is one of the most common products of putrefaction, but is wholly inert.

Sapin, $C_5H_{14}N_2$.—This base is isomeric with cadaverin and neuridin, and is without poisonous action.

Hexamethylenediamin, $C_6H_{16}N_2$.—Found by Garcia in a decomposing mixture of pancreas and muscle. Physiologically it is probably inert.

Unnamed Base, $C_7H_{10}O_2$.—This is a basic substance formed during the alcoholic fermentation of crude sugars. It is not known to be possessed of any medical interest.

Susotoxin, $C_{10}H_{26}N_2$ (?).—Novy obtained this ptomaïn from cultures of the bacillus of hog-cholera. It is feebly poisonous. One hundred milligrams administered to a small rat caused convulsive tremors and death after one and one-half hours. Section showed the heart in diastole, the lungs anæmic, the stomach contracted, and the subcutaneous tissue pale and œdematous.

Methyl Guanidin, $C_2H_7N_3$.—This base has long been known as an oxidation product of kreatin and kreatinin, and several bacilli have the power of originating it. It has been found in cultures of the bacilli of anthrax and Asiatic cholera, as well as in tissue undergoing disintegration through the agency of the ordinary putrefactive bacteria. In its physiological action, the putrefactive base is identical with that prepared synthetically. It causes dyspnœa, muscular tremor, and general convulsions. Brieger reports the following observation on a guinea-pig to which 0.2 gm. of methyl guanidin had been administered subcutaneously: The respirations at once became more rapid; there were free discharges of urine and fæces; the pupils rapidly dilated to the maximum and came to rest; the animal became motionless, although not paralyzed; respirations grew deeper and more labored; dyspnœa set in, the animal fell upon its side, and died

after general clonic convulsions within twenty minutes after the administration. Section showed the heart in diastole, the intestines filled with fluid, the bladder contracted, and the cortex of the kidney hyperæmic, but the papillæ pale.

Morrhuin, $C_{19}H_{27}N_3$.—This substance constitutes about one-third of the total bases found in cod-liver oil. It is said to be both diaphoretic and diuretic. Twenty-nine milligrams administered to a guinea-pig caused a loss of 13.5 gm. in weight within two and one-half hours. However, its toxic action is not marked, and the lethal dose has not, so far as I know, been determined.

Unnamed Base, $C_{13}H_{20}O_4$.—This base was obtained by Oser in the fermentation products resulting from the action of yeast on pure cane sugar. It probably possesses no medicinal or physiological importance.

Unnamed Base, $C_{17}H_{38}N_4$.—This substance was obtained by Gautier and Etard from decomposing matter, but its properties have not been studied sufficiently to indicate whether or not it is of importance.

Asellin, $C_{25}H_{32}N_4$.—This is one of six bases that have been found in cod-liver oil. In large doses it is said to cause rapid respiration and stupor.

Mydin, $C_8H_{11}NO$.—This is a non-poisonous base obtained from the decomposing viscera of man. It is strongly ammoniacal and acts energetically as a reducing agent.

Neurin, $C_5H_{13}NO$.—This substance was first obtained by Liebreich by boiling protagon with concentrated baryta. Since then it has been found in decomposing animal tissue from diverse sources. The free base has a strongly alkaline reaction, and when brought into contact with vapor of hydrochloric acid forms a white cloud. Neurin is intensely poisonous, resembling muscarin in its action. In frogs very small amounts cause complete paralysis of the extremities. Respiration ceases first, and the heart beats more and more feebly, and finally stops in diastole. If at this point atropine be injected, the heart begins to beat again. Frogs previously atropinized bear poisonous doses without ill effect. In rabbits there is abundant flow of saliva and of the secretions from the nose and eyes. At first the heart beat seems to be strengthened, then it slows down, and stops in diastole. The peristaltic movements of the intestines are increased and profuse diarrhœa results. Death is often preceded by violent convulsions.

Cholin, $C_5H_{15}NO_2$.—Cholin was first obtained from bile. It has since been found to be widely distributed both in vegetables and animals, being present in toadstool, hops, hempseed, lentils, white

mustard, ergot, in nuts of different kinds, in the seed of vetch, peas, beans, lupines, etc., also in the yolks of eggs, in the brain, blood, lungs, heart, etc. As a decomposition product it is frequently met with. Cholin, while not wholly devoid of poisonous properties, is toxic only in large doses, and the chief interest attached to it in our present study lies in its close relationship to neurin. By giving up a molecule of water, the comparatively inert cholin may be transformed into the highly poisonous neurin. This decomposition would easily explain the rapid development of poisonous properties in ordinary foods, known to occur occasionally. On the other hand, it has been suggested that in attempts to isolate ptomaïns, neurin may be formed by the action of the chemical reagents employed on the cholin, and thus the chemist in attempting to find a poison may bring one into existence. That neurin may be prepared from cholin by purely chemical agencies is a demonstrated fact. However, the known means necessary to accomplish this conversion are not those employed in toxicological research, and at the present writing the supposition that the chemist may generate neurin from cholin in the process of analysis seems to be unwarranted. On the other hand, Schmidt found that cholin chloride, when allowed to stand for fourteen days with hay infusion or with dilute blood, is almost wholly decomposed, yielding trimethylamin and a base, the platinochloride of which resembles the corresponding compound of neurin, with which the free base agrees in its poisonous properties. It will thus be seen that the conversion of the feebly poisonous base into the more poisonous one may be accomplished by bacterial activity. The neurin-like effects of certain samples of poisonous milk and milk products is certainly suggestive of the possibility of the presence of neurin in them.

In very large doses cholin has the same action as neurin. Brieger found it necessary to give 0.1 gm. of cholin chloride to induce in a rabbit of the same weight the effects obtained by the use of 0.005 gm. of the corresponding salt of neurin. He also ascertained that the fatal dose of cholin per kilogram of body weight was about 0.5 gm., which is ten times the fatal dose of neurin.

A Base, $C_5H_{11}NO_2$.—This substance was isolated by E. and H. Salkowski from decomposing meat and fibrin. It is probably identical with δ-amido-valerianic acid, and is not known to be of etiological importance.

Betain, $C_5H_{13}NO_3$.—This is oxyneurin, and its distribution is almost as wide as that of cholin. However, it is non-poisonous, and consequently does not take an important place in the present inquiry.

Muscarin, $C_5H_{15}NO_3$.—This is the well-known active principle of

poisonous mushroom. It is closely related to cholin, from which it may be formed by the oxidizing action of strong nitric acid. As a bacterial product, muscarin has been obtained from decomposing haddock and from horse-flesh. The bacterial muscarin seems to be identical with that from toadstools, but shows some difference in physiological action from the synthetically prepared base. Thus Böhm found that the synthetical base paralyzes the intramuscular nerve endings, and, according to Meyer, only 0.1 mgm. is necessary to accomplish this result, while the natural base is said not to have this effect. In frogs small doses of muscarin induce total paralysis, arresting the heart in diastole. When the effects of muscarin have been induced in animals they may be arrested by atropine, but frogs previously atropinized are still susceptible to muscarin. In rabbits small doses cause salivation, lacrymation, contraction of the pupils, profuse diarrhœa, and finally death preceded by convulsions.

Mydatoxin, $C_6H_{13}NO_2$.—This compound was obtained by Brieger from large quantities of human viscera allowed to decompose for months, also from putrefying horse-flesh. Upon most animals this base manifests only feebly toxic action. White mice are, however, more susceptible. Small doses cause in these animals lacrymation, diarrhœa, dyspnœa, convulsions, and death.

A Base (?), $C_6H_{13}NO_2$.—This is an isomer of mydatoxin. However, it is not positive that this is a base, since there are certain reasons for believing that it is an amido-acid. It is not known to be poisonous.

Mytilotoxin, $C_6H_{15}NO_2$.—This is the specific poison found by Brieger in poisonous mussels. It induces all the characteristic phenomena observed in those who have partaken of this article of diet when the mussels have acquired harmful properties. It resembles curare in its action, causing paralysis. The symptoms will be discussed at greater length when we reach the subject of poisonous foods.

Gadinin, $C_7H_{17}NO_2$.—This base has been found in decomposing haddock and gelatin, also in pure cultures of proteus vulgaris. Gadinin is poisonous only when employed in large quantities.

Typhotoxin, $C_7H_{17}NO_2$.—This base, which is isomeric with gadinin, was discovered by Brieger in cultures of the Eberth bacillus, and was for a while believed to be the chief chemical factor in the causation of typhoid fever. However, it is now known that this bacillus has among its chemical products a more energetic poison than this ptomaïn. In fact, typhotoxin seems not to be a constant product of the growth of the typhoid bacillus. Whether it appears in cultures of this germ or not, depends upon the nature of the medium and the

temperature at which the growth occurs. The physiological action of this base has been studied only on guinea-pigs and mice. In these it induces quickened respiration, accompanied by salivation. The muscles fail to support the animal, and it falls upon its side. The pupils dilate and cease to react. The heart-beat and respiration gradually fail, and death occurs within from one to two days. Diarrhœa accompanies the above-mentioned symptoms. The intestines are found to be contracted, the lungs are hyperæmic, while other internal organs are pale. The heart stops in diastole.

A Base (?), $C_7H_{17}NO_2$.—Obtained by Brieger from decomposing horse-flesh, and probably identical with the body separated by Baginsky and Stadthagen from cultures of a bacillus found in the stools of a child suffering from cholera infantum. This compound, after the most thorough washing, gives an acid reaction, but it does not combine with bases. It has been supposed to be an amido-acid, but it differs from this group in being poisonous and in failing to give a red coloration when treated with ferric chloride. With the exception of its reaction, it acts like a base, forming both simple and double salts. Its action on frogs is like that of curare. Paralysis comes on speedily. The pupils dilate and the heart's action becomes gradually weaker, until this organ stops in diastole. Guinea-pigs require considerable doses, from 0.05 to 0.3 gm. When this amount is given the respirations are increased. The pupils at first contract and then dilate and become reactionless. Evident chills follow one another in rapid succession. The temperature falls below the normal. Lacrymation and salivation are observable, but not so profuse as under the muscarin-like ptomaïns. Convulsions occur. The temperature continues to fall, and the ears, previously engorged, become pale and cold. The heart-beats become weak and irregular. A condition of general paralysis supervenes, but stimuli may cause convulsions. Finally the paralysis becomes complete and death results. The intestines are pale and contracted, and the heart stops in diastole.

Morrhuic Acid, $C_9H_{13}NO_3$.—This compound has both basic and acid properties. In reaction it is acid, but it combines with acids forming salts. This substance, together with butylamin, amylamin, hexylamin, dihydrolutidin, asellin, and morrhuin, is found in cod-liver oil. All of these together make up about 0.2 per cent. of this oil. They are regarded by Gautier, their discoverer, as true leucomaïns dissolved from the hepatic cells by the oil. However, it is more probable that they are products of initial decomposition, starting in the liver before the extraction of the oil. Bouillot finds evidence of their existence in microscopical sections of the liver. Morrhuic acid is a resinous body, but may be obtained in crystalline

prisms. There has been, so far as I know, no study of its physiological action.

Tetanin, $C_{13}H_{30}N_2O_4$.—This base was discovered by Brieger in mixed cultures of the tetanus germs of Rosenbach, and was found later by Kitasato and Weyl in pure cultures of the tetanus bacillus. From 1¼ kgm. of beef used in the culture they obtained 1.7118 gm. of tetanin hydrochloride—a yield of 0.137 per cent. The symptoms induced by comparatively large doses of this substance in rabbits, guinea-pigs, and mice may be divided into two stages. In the first, the animal becomes lethargic and seems to be partially paralyzed; in the second the characteristic convulsions of tetanus set in and terminate in death. It should be understood, however, that the most potent of the chemical products of the tetanus bacillus is not a ptomaïn.

A Base, $C_{14}H_{20}N_2O_4$.—This compound was obtained by Guareschi from putrid fibrin. Nothing is known of its physiological action.

A Base, $C_7H_{18}N_2O_6$.—Discovered by Pouchet; it has been but imperfectly studied.

A Base, $C_{16}H_{23}N_2O_4$. — Obtained by Lepierre from poisonous cheese. When fed to guinea-pigs it causes diarrhœa. Fifty milligrams injected intravenously into a rabbit produced no effect.

Tyrotoxicon or Tyrotoxin.—This substance has never been obtained in sufficient quantity to enable one to determine its ultimate composition. It has been found in poisonous cheese and other milk products. Chemically it is very unstable, and when its aqueous solution is heated to 90° C. it decomposes. It causes constriction of the throat, nausea, vomiting, purging, and marked prostration. Further statements concerning its action will be made in the discussion of poisonous cheese. It should be distinctly understood that this is not the only active agent, probably not the most important one, in poisonous cheese. Recent studies have convinced me that this base is not present in the majority of samples of poisonous cheese.

Mydalein.—This is another ptomaïn whose composition has not been determined. It was found by Brieger in putrefying cadaveric organs, liver, spleen, etc. Mydalein seems to have a specific action. Small doses injected into guinea-pigs cause an abundant secretion from the nose and eyes. The pupils dilate, reach a maximum, and then become reactionless. The temperature rises from 1° to 2° C. During this action of the poison the animal seems to be in a somnolent condition, and the peristaltic movement of the intestines is increased. Later the temperature declines to the normal, and the pulse and respiration, both of which had been quickened, return to

the normal, and the animal recovers. With larger doses death may result. In these cases the intestines are found contracted and the heart is in diastole.

A Base.—The composition of this body, obtained from decomposing viscera, has not been ascertained. In guinea-pigs it causes free purgation which may continue for several days, leading to great weakness and depression, but terminating in recovery.

Pyocyanin, $C_{14}H_{14}N_2O$.—This is the blue coloring matter of pus, and is a special product of the bacillus pyocyaneus.

Peptotoxin.—This is the name given by Brieger to a substance found by him in peptone, also in putrefying brain, liver, muscle, casein, and fibrin. Salkowski claims that peptotoxin has no existence. In eight digestive experiments with fresh fibrin, he obtained a poisonous extract in only one instance. Peptic digestion of other albuminous substances also yielded negative results. However, whether peptotoxin as described by Brieger exists or not, there can scarcely be any difference of opinion on the following points: 1. With fresh food to act upon and with normal gastric juice to act, the process of peptic digestion proceeds without the formation of any harmful substance; 2. With putrid food, containing poisons to start with, the most active digestion does not guarantee the destruction of these poisons; 3. With even the best of food, peptic digestion may proceed so slowly and imperfectly that during the process poisons may be formed by bacterial agencies.

In addition to the ptomaïns already briefly discussed, investigators have met with numerous others, which have been found in quantities too small to admit of any thorough study. From both aqueous and alcoholic extracts of cultures of the staphylococcus pyogenes aureus, Leber obtained a crystalline body which he named phlogosin. There is some doubt about the presence of nitrogen in this substance, and since it blackens silver it is supposed to contain sulphur. Very small quantities of phlogosin applied to the conjunctiva set up an inflammation that may continue to suppuration and necrosis. When introduced into the anterior chamber of the eye it leads to suppuration and keratitis. From cultures of the same bacillus Brieger obtained traces of a base different from phlogosin.

Gram allowed yeast mixed with an infusion of hay to ferment for fourteen days; at the expiration of this time he obtained from the mixture a poisonous extract that induced paralysis in frogs.

Guareschi and Mosso obtained from fresh meat extracted by Dragendorff's method a substance that gives the general alkaloidal reactions. This demonstrates the need of exercising the greatest care in the detection of the vegetable alkaloids in toxicological examinations.

From poisonous mussels Brieger obtained small quantities of a base, along with the mytilatoxin, that induced profuse salivation in animals.

Bacterial Proteids.

The study of any proteid is a difficult task. Indeed, we are not as yet positive about the ultimate composition of a single member of this group, and so far as molecular structure is concerned we are quite in the dark. While this is true of all proteids, those of bacterial origin have certain special difficulties in the way of an understanding of their chemistry. Theoretically at least we may divide the bacterial proteids into two classes: (1) Those which constitute or have constituted an integral part of the bacterial cells; and (2) those which have not been assimilated by the cell, but which have been formed by the fermentation or cleavage action of the bacteria on the proteids in which and on which they are growing. The separation of the proteids of these two classes has not been accomplished, and practically such a separation must be, for the present at least, quite impossible in a quantitative way. We allow bacteria to grow for any length of time in a nutrient solution. We then attempt to separate the soluble from the insoluble proteids by filtration through porous tile. We try in this way to separate the cells from the soluble contents of the medium, but we have learned that the solubility of proteids is a relative matter, dependent upon a great variety of conditions, such as the presence of inorganic salts, the temperature, the size of the molecule, etc. The result is that our separation is very incomplete. There remain on the filter not only the bacterial cells, but extracellular proteids. Therefore an analysis of the detritus left on the filter gives us no exact information of the constituents of the living cells. In many cultures there are mucilaginous extracellular proteids that fail to pass through even the relatively larger pores of coarse filter paper, which are soon filled with this material, and the filtration of more soluble substances is arrested. On the other hand, the filtrate may contain the following proteid bodies: 1. Those portions of the soluble proteids which were used in the preparation of the culture, and which have escaped the action of the bacteria; 2. Proteids which have been at one time integral parts of the cells, but which have passed into solution on the death and dissolution of the cells; 3. Proteids that have been formed by the fermentation or cleavage action of the bacteria on the constituents of the nutrient solution.

There is no evidence at the present time (1897) that any of the proteids formed by the cleavage action of bacteria on the proteids of

the nutritive medium or on those of the animal body are specific factors in the causation of disease. As has been elsewhere stated, many bacteria have a peptonizing action, but the peptones thus formed are not known to be any more poisonous than those that result from the action of the gastric juice. Moreover, the amount of peptone formed by bacteria in the animal body must be so small that this product cannot be considered as of importance in the study of bacterial poisons. The peptonizing properties of bacteria may be of significance in the destruction of tissue, but probably not otherwise. As will be seen later, the weight of evidence at present is in favor of the theory that the specific bacterial poisons are formed by synthetical rather than by analytical processes.

Bacterial Cellular Proteids.

In old cultures, especially in those of bouillon, the bacteria form a sediment. Many of the cells in such deposits are dead and a part of their contents has passed into solution, while others are still possessed of life and the capability of growth and reproduction. No one would claim that a study of the chemical composition of these bacterial deposits would give the exact composition of the living cells, but such analyses furnish us with the only information now possessed concerning the bacterial cellular proteids. Nencki was the first to attempt to advance knowledge in this way. The material on which he worked consisted of deposits of putrefactive bacteria. These were obtained by decantation of the supernatant fluid, washed with ether in order to remove the fat, dissolved in fifty parts of 0.5 per cent. solution of caustic potash, heated for some hours at 100° C. and filtered. The filtrate was acidified with dilute hydrochloric acid and the precipitation completed by the addition of rock salt. The precipitate was washed first with saturated salt solution, dried at 100° C., and then washed free from salt with water and again dried. An ultimate analysis of the product thus obtained indicated the formula, $C_{25}H_{42}N_6O_9$. However, no claim can be made that this is a definite chemical compound. Nencki suggested that this substance be designated by the term "mycoprotein," and described its properties as follows: The freshly precipitated body is soluble in water, dilute acids, and alkalies, but after being dried at 100° C. it loses its solubility in water. The aqueous solution is acid in reaction. From its solutions mycoprotein may be precipitated by picric and tannic acids, by mercuric chloride, and other general alkaloidal reagents. It is not precipitated from aqueous solution by alcohol. Nencki found that his mycoprotein did not give the xanthoproteic, but did give the biuret and Millon reactions. According to Schäffer, it is

changed into peptone by acids, and on being fused with five parts of caustic potash it is decomposed, yielding ammonia, amylamin, phenol (0.15 per cent. of its weight), valerianic acid (38 per cent.), leucin, and traces of indol and skatol.

It was at first believed that the cellular proteids of bacteria are inert, but more recent investigations have shown that this assumption is not well founded. It has been found that they are not always inert, and that they differ according to their origin. The purified pyogenic proteid obtained from the pneumonia bacillus of Friedländer by Buchner was found to give the following reactions: It is soluble in water and the concentrated mineral acids, and readily soluble in dilute alkalies. From solutions in alkali it is precipitated on the addition of an acid. From its aqueous solution it is not precipitated by boiling nor by saturation with common salt, but is precipitated by magnesium sulphate and the general alkaloidal reagents, also by absolute alcohol.

Bacterial Toxins.

As has been stated, it is evident that the basic products of bacterial growth will not account for the virulence of cultures of many of the pathogenic germs after the removal of the living bacteria. The ptomaïns are not present in sufficient quantity, nor are they possessed of sufficient toxicity to be considered as the only or even as the most potent bacterial products. Moreover, in cultures of some germs, and among these are those whose cultures are highly poisonous, no ptomaïns have been formed. This is true of diphtheria. Loeffler, Roux and Yersin, and Brieger and Fraenkel failed to find any active basic body in sterilized cultures of the diphtheria bacillus, notwithstanding the fact that these cultures were found to be possessed of remarkably poisonous properties. Moreover, while Brieger had succeeded in obtaining several poisonous ptomaïns from cultures of the tetanus bacillus, all of these combined could not account for the intensity of the action of cultures of this bacillus, freed from the living microorganism by filtration through porcelain. What, then, is the nature of the powerful agents that are elaborated in cultures of the bacteria of tetanus, diphtheria, and of the other infectious diseases, and to which the symptoms of these diseases and death from them are due? Roux and Yersin suggested that the active poison of diphtheria might be a ferment. Brieger and Fraenkel at first held that it was a poisonous proteid, and suggested that non-basic bacterial poisons might be best designated as "toxalbumins." They then believed that these "toxalbumins" originated in the splitting up of the proteids of the culture medium or of proteids in the animal body

by the fermentative action of the bacteria. However, more recent studies, especially those of Brieger, indicate that the two facts most positively proven in regard to the toxins are: (1) That they are not albumins; and (2) that they are not formed by analytical process, but are formed along synthetical lines.

In 1893 Brieger and Cohn demonstrated that the tetanus toxin, in the purest form in which they could obtain it, contains no phosphorus and only unweighable traces of sulphur. The latter of these was supposed to be due to the ammonium sulphate used in precipitation. In 1895 Brieger made an ultimate analysis of the tetanus toxin, purified so far that 0.00000005 gm. kills mice with all the symptoms of the disease, with the following results: Carbon, 52.08 per cent.; hydrogen, 8.1 per cent.; nitrogen, 15.71 per cent. Purified to this extent, this toxin is not precipitated by ammonium sulphate, thus showing that in the preceding researches it had been carried down mechanically by this reagent with certain proteids. It gave the biuret reaction so imperfectly that Brieger felt justified in the belief that the coloration was not due to the toxin, but to some adherent proteid impurity.

In 1896 Brieger and Boer attempted the isolation of the toxins of diphtheria and tetanus. They state: "If filtered bouillon cultures of diphtheria or tetanus be treated with mercuric chloride, zinc sulphate, or still better, with zinc chloride, the toxins are quantitatively precipitated. Since these precipitates are wholly insoluble in water, they can be thoroughly washed. By dissolving these washed double compounds in water containing common salt or a trace of alkali, the presence of all the toxin can be demonstrated (by experiments upon animals ?). On attempting to separate the zinc from the toxin by passing a current of carbonic-acid gas through an alkaline solution, the combination remains unbroken. Hydrogen sulphide cannot be employed because it destroys the toxin. The purified zinc compound of the toxin contains no trace of albumin or peptone. A so-called albumin derivative in the usual sense of that term is not present in the toxin of diphtheria and tetanus. A litre of diphtheria or tetanus bouillon yields about 3 gm. of the dried zinc compound, and this contains only about 0.3 gm. of organic matter which must include the whole of the toxin. The zinc compound is not precipitated by ammonium sulphate, phosphomolybdic acid, or phosphotungstic acid, but is precipitated by carbonic acid. The absence of the xanthoproteic, the biuret, and the Adamkiewicz reactions, the failure to give a red coloration on being boiled wth Millon's reagent, and the failure to affect polarized light in either direction show that there is present no peptone, albumose, or albuminate. On being boiled with ferric

chloride there is a markedly red coloration. Whether this be due to unimportant admixture with amido-acids or not must be determined by future investigations, which must also take into consideration the possibility of their being ferments."

The facts already mentioned show that specific bacterial poisons, now generally known as "toxins," are not proteid bodies. As is well known, the word toxin means a poison, and all poisons might be called toxins, but I shall employ this term to indicate the specific bacterial poisons, the chemical classification of which remains for the present impossible on account of want of knowledge concerning them. It is better to employ some general term than to adopt a name which later investigations might show to be inapplicable. While it is true that the poisonous ptomaïns are bacterial toxins, they will be separately designated in this article.

It has already been stated that the toxins are formed by synthetical processes and not by splitting up the constituents of the culture medium or those of the animal body. Uschinsky materially advanced our knowledge of the physiology of bacteria by demonstrating this fact. He has grown some of the most important pathogenic bacteria, including those of cholera, diphtheria, tetanus, and typhoid fever, in the following menstruum:

	Parts.
Water,	1,000
Glycerin,	30–40
Sodium chloride,	5–7
Calcium chloride,	0.1
Magnesium sulphate,	0.2–0.4
Dipotassium phosphate,	2–2.5
Ammonium lactate,	6–7
Sodium asparginate,	3–4

From cultures of the above-mentioned bacteria in this and similar media, he has obtained toxins not less virulent than those found in bouillon peptone. This demonstrates that the germ constructs its toxin out of bodies of less complex structure.

It is not my purpose to discuss the individual toxins at this time. This will be more appropriately done in connection with a discussion of the chemical poisons of the different diseases, which will be taken up later.

Toxicogenic and Pathogenic Bacteria.

All bacteria that are harmful to man produce poisons, and consequently they may be designated as toxicogenic. All pathogenic bacteria are toxicogenic, but there might easily be difference of opinion on the question whether or not all toxicogenic germs are pathogenic. There are saprophytic bacteria which will not grow at the temperature

of the body, but when developed in milk and other foods at a lower temperature they elaborate chemical poisons. These bacteria can hardly be called pathogenic, and yet in this indirect way they may cause death. There are other obligate saprophytes which may produce poisons in food both before and after it has been taken into the alimentary canal. The food in the duodenum has no more vitality than it has in the nursing-bottle of the infant. Moreover, the excretions poured into the intestines are not supposed to be possessed of any vitality. A germ that will grow on a certain medium in a flask and produce a poison may grow on the same medium in the intestines and produce the same poison, provided it is not destroyed or modified by the temperature or by some secretion of the body.

In studying the bacterial poisons I think that it will be found convenient to divide them into two groups, according to the bacteria elaborating them. These groups are: (1) The poisons of the saprophytic bacteria; and (2) those of the specific pathogenic bacteria. Since the bacterial poisons of the first of these groups are generally introduced into the body with food, they will be discussed under the head of Food Poisoning, and the poisons produced by the pathogenic bacteria will be discussed subsequently.

FOOD POISONING (BROMATOTOXISMUS*).

Within a few years past the medical profession has ascertained that ordinary foods frequently undergo changes that may render them harmful. These untoward effects may be due to any of the following causes:

---

* The introduction of a new subject in the line of scientific investigation sometimes calls for the adoption of new terms. This demand seems to me to be evident in a discussion of food poisoning. I have therefore attempted in this article to introduce certain new terms. In doing this I have not relied upon myself, but have consulted with my classical colleague, Prof. Francis W. Kelsey, whose reputation in philological studies is sufficient guaranty that these words are etymologically correct. The following is a glossary of the new words employed in this article:

Bromatotoxismus, *βρῶμα* (*βρώματος*), food, and *τοξικόν*, poison. Food poisoning or poisoning with food.

Bromatotoxicon. A general term for the active agent in a poisonous food.

Bromatotoxin. A basic poison generated in food by the growth of bacteria or fungi.

Galactotoxismus, *γάλα* (*γάλακτος*), milk. Milk poisoning.

Galactotoxicon.

Galactotoxin.

Ichthyotoxismus, *ἰχθύς*, fish.

Ichthyotoxicon.

Ichthyotoxin.

Kreotoxismus, *κρέας* or *κρέως*, meat poisoning.

1. Grains may become infected with parasitic fungi that are poisonous. This is the cause of epidemics of ergotism.

2. Both plants and animals may feed upon substances which are not harmful to them, but which may seriously affect man on account of his greater susceptibility. It is said that birds which have fed upon the mountain laurel furnish food poisonous to man.

3. The flesh of some animals is poisonous during the period of physiological activity of certain glands. Some fish are poisonous during the spawning season.

4. Any food may be infected with specific germs and serve as the carrier of the infection. The distribution of typhoid fever through the can of the milkman is a matter of occasional observation.

5. The animal may be afflicted with a specific disease, and this may be transmitted to man in the meat or milk. This is one of the active agencies in the spread of tuberculosis.

6. Foods of various kinds may become contaminated with saprophytic bacteria, which by their growth elaborate chemical poisons either before or after the food has been eaten.

Some of the above-mentioned forms of food poisoning will hardly come within the scope of this paper, while others will have only incidental mention. I shall endeavor to present the subject in that form which will be of greatest interest and benefit to the practitioner.

Mussel Poisoning (Mytilotoxismus).

There are three apparently quite different classes of symptoms induced by poisonous mussels. In a given case there may be individual symptoms representing each of the three kinds, but there is generally a preponderance of those of one group.

Kreotoxicon.

Kreotoxin.

Mytilotoxismus, *μυτίλοι*, a sea-mussel. Mussel poisoning. Used already by Husemann.

Mytilotoxicon.

Mytilotoxin. The name given by Brieger to the ptomaïn discovered by him in poisonous mussel.

Sitotoxismus, *σῖτος*, cereal food. Poisoning with vegetable food.

Sitotoxicon.

Sitotoxin.

Tyrotoxismus, *τυρός*, cheese. Cheese poisoning. Used already by Husemann.

Tyrotoxicon.

Tyrotoxin.

Husemann uses the word zootrophotoxismus to indicate poisoning with animal food. The same author has employed the word halichthyotoxismus to designate poisoning with fish.

Mytilotoxismus gastricus sive intestinalis is that form of mussel poisoning in which the symptoms are practically identical with those of cholera nostras. There is at first nausea, followed by vomiting, which may continue for hours. At first the vomit consists of food, but later there is nothing but mucus tinged with bile, and in severe cases with blood. The purging is usually accompanied with great tenesmus and pain. The pulse becomes rapid and weak. Fodéré reports a case of this kind in which death occurred on the second day. Section showed the mucous membrane of the stomach and small intestines highly inflamed and containing an excess of mucus.

Mytilotoxismus exanthematicus is the form most frequently observed. The symptoms seem to be largely due to nervous disturbances. There is a sensation of heat, which usually begins in the eyelids, then spreads to the face and may extend over the entire body. This sensation is followed by an eruption usually called nettlerash, although it may be papular or vesicular. The itching is said to be quite intolerable. Usually after the eruption, though sometimes before, the breathing becomes labored. These symptoms may be accompanied by slight disturbances of the stomach and bowels, or vomiting and purging may be wholly absent. Mohring has reported cases of this kind in which the dyspnœa early became great, the face grew livid, the extremities showed convulsive movements, consciousness was soon lost, and death occurred within three days.

Mytilotoxismus paralyticus is the form that has been most thoroughly studied. As early as 1827 Combe reported cases of this kind, as he had under observation thirty persons poisoned with mussels. His description is as follows: "None, so far as I know, complained of anything peculiar in the smell or taste of the animals, and none suffered immediately after taking them. In general, an hour or two elapsed, sometimes more; and the bad effects consisted rather in uneasy feelings and debility than in any distress referable to the stomach. Some children suffered from eating only two or three; and it will be remembered that Robertson, a young and healthy man, took only five or six. In two or three hours they complained of a slight tension of the stomach. One or two had had cardialgia, nausea, and vomiting; but these were not general or lasting symptoms. They then complained of a prickly feeling in their hands, heat and constriction of the mouth and throat, difficulty of swallowing and speaking freely, numbness about the mouth gradually extending to the arms, with great debility of the limbs. The degree of muscular debility varied a good deal, but was an invariable symptom. In some it merely prevented them from walking firmly, but in most of

them it amounted to perfect inability to stand. While in bed they could move their limbs with tolerable freedom, but on being raised to the perpendicular position they felt their limbs sink under them. Some complained of a bad coppery taste in the mouth, but in general this was in answer to what lawyers call a leading question. There was slight pain of the abdomen, increased on pressure, particularly in the region of the bladder, which organ suffered variously in its functions. In some the secretion of urine was suspended; in others it was free, but passed with pain and great effort. The action of the heart was feeble; the breathing unaffected; the face pale, expressive of much anxiety; the surface rather cold; the mental faculties unimpaired. Unluckily the two fatal cases were not seen by any medical person, and we are therefore unable to state minutely the train of symptoms. We ascertained that the woman, in whose house were five sufferers, went away as in a gentle sleep, and that a few moments before death she had spoken and swallowed."

Post-mortem examination of the fatal cases showed no abnormality.

Schmidtmann has reported the symptoms observed by himself in some workmen and members of their families, who had partaken of mussels taken near a newly constructed dock. The mussels had been cooked. The appearance of the symptoms varied with the amount eaten. Those who ate freely of this article showed the first effects within less than an hour, while those who partook more sparingly were affected later and less severely. There was a sensation of constriction in the throat, mouth, and lips; the teeth were set on edge, as though sour apples had been eaten. The sufferers complained of headache and dizziness, and experienced a sensation of flying and an intoxication similar to that produced by alcohol. The pulse was incompressible and rapid, 80 to 90 per minute. There was no elevation of temperature, and the pupils were dilated and reactionless. Speech was difficult, broken, and jerky. It was said that the limbs were heavy. The hands grasped at objects spasmodically and missed their aim. On attempting to stand, it was found that the legs could not support the body. There were nausea and vomiting, but no abdominal pain or diarrhœa. The hands and feet became numb and cold, and these sensations soon extended over the entire body. In some the body was covered with a cold, clammy sweat. There was some uneasiness induced by the nausea and a sensation of suffocation, then came on a quiet sleep. One person died in one and three-quarter hours, another in three and one-half hours, and a third in five hours, after eating of the mussels.

In one of the fatal cases marked hyperæmia and swelling of the

mucous membrane of the intestines were observed, and were regarded by Virchow as sufficient to be designated as an enteritis. The spleen was said to be enormously enlarged, and the liver showed numerous hemorrhagic infarctions. It is rather difficult to see how the spleen could become enormously enlarged in a few hours. The heart was empty, but the blood-vessels of the viscera were observed to be distended.

Cats and dogs partook of these cooked mussels and developed symptoms similar to those observed in the men; and a rabbit treated with the water in which the mussels had been boiled died very quickly.

There has been great variety of opinion expressed concerning poisonous mussels. Some have claimed that there are certain species that are constantly poisonous, and that these are often found with the edible kinds. Virchow and Schmidtmann attempted to describe the poisonous species, stating that it has a brighter shell, a sweeter, more penetrating, bouillon-like odor than the edible kind, and that the flesh of the former is yellow and the water in which they are boiled becomes bluish. The belief in a poisonous species has been championed by others; but Möbius has clearly pointed out the fallacy of this. He has shown that the color and brilliancy of the shell varies with the amount of salt in the water, its temperature, whether it is still or running, and the character of the bottom; also that the difference in color of the flesh is due to sex. The sexual glands which form the greater part of the mantle are yellow in the female and white in the male.

It has been suggested that the mussels absorb copper from the bottoms of vessels, but Christison tested the mussels that affected Combe's case, with negative results, and also pointed out the fact that the symptoms were not those of poisoning with copper.

It was held by Edwards that the ill effects were due to idiosyncrasies in the consumers; but when all who partake of the food, including cats and dogs, manifest the same symptoms, the absurdity of this assumption becomes evident.

De Beume found some medusæ in the vomit of a person suffering with mussel poisoning, and attributed the untoward effects to these; but there was no evidence that these medusæ were poisonous, and, moreover, they are not constantly associated with poisonous mussels.

The theory of Burrow, that all mussels are poisonous during the period of reproduction, has met with general popular credence, and has been applied to all mollusks. It is upon this theory that the popular superstition that shellfish should not be eaten during months in the name of which the letter "r" does not occur, is founded.

This superstition at one time took the form of a legal enactment in France, forbidding the sale of shellfish from the 1st of May to the 1st of September, but this restriction has been removed. The only grain of truth in this popular idea lies in the fact that these are the warm months, when decomposition is the more likely to alter food injuriously. People have, however, been poisoned with mussels at all times of the year.

There can now be but little doubt that the gastrointestinal and exanthematic forms of mytilotoxismus are due to putrefactive processes, while the paralytic manifestations of the disease are due to the ptomaïn isolated by Brieger and named by him mytilotoxin. The toxicological action of this ptomaïn has already been given (see page 17).

Why certain mussels should contain mytilotoxin while others do not, is a question about the answer to which there might still be some difference of opinion. It would seem, however, that any mussel may acquire this poison when it lives in filthy water. Schmidtmann and Virchow have ascertained that edible mussels may become poisonous when left for fourteen days or longer in filthy water, and, on the other hand, poisonous mussels may become edible if kept for four weeks or longer in clear sea water. Whether the animals become diseased or not in filthy water, is not known. Cases of mytilotoxismus have several times occurred among those eating mussels taken from Wilhelmshaven, the place that supplied Brieger with the material from which he obtained mytilotoxin. Schmidtmann has found that good mussels placed in the water of this harbor soon become poisonous, and that the poisonous mussels of this bay lose their toxic properties when placed in the open sea. Lindner has found in the water of Wilhelmshaven and in the mussels taken from the same a great variety of bacteria, amœbæ, protozoa, and other low forms of life. He also states that non-poisonous mussels placed in filtered water from this source do not become poisonous. From this he concludes that the animals become infected in the water of this harbor. Cameron makes a somewhat similar statement about the poisonous mussels near Dublin, taken from water contaminated with sewage. He found that the livers of these animals were much enlarged, and from them he obtained a base that is probably identical with mytilotoxin.

That mytilotoxin is not an ordinary putrefactive product is shown by the fact that Brieger failed to detect its presence in mussels that had been allowed to decay.

That oysters taken from beds near the outlet of sewers may become contaminated with the specific germ of typhoid fever has been

pretty well demonstrated within the past few years, but this subject hardly belongs to a discussion of the chemical poisons produced by the bacteria. However, it is altogether probable that oysters may become poisonous in the same way that mussels acquire harmful properties. Pasquier has reported cases of oyster poisoning from animals taken from a bed at Havre near the outlet of a drain from a public watercloset. Oyster broth made with milk may develop any of the bacterial poisons that are elaborated in milk.

The most important form of treatment of mytilotoxismus should be *prophylaxis;* but, like the preventive treatment of many other kinds of poisoning, it is generally administered *post factum.* However, there should be police regulations against the sale of all kinds of mollusks and of all fish as well taken from filthy waters. Certainly attention should be given to localities that have once supplied poisonous food of this kind. Many popular rules have been given for the easy recognition of poisonous mussels, and to some of them has been given credence by medical authors. An unusually large mussel is regarded with suspicion, and Lohmeyer gives measurements that may guide the person in search of this article of food. Stress is placed on color by some, and one is advised to avoid the dark-brown-blue, and to purchase the dark-blue or the dark-green-blue. We may expect to see the prudent hungry man draw from his pocket a scale of colors and carefully compare it with the shell of the juicy bivalve before he assigns it to his digestive organs, if he is to observe the rules laid down in some recent medical works. Then he will take the dimensions of the whole, measure the thickness of the shell, and test its strength, for we are informed that the poisonous clam has a thin, brittle shell. Seriously, one is to avoid shellfish from impure waters, and he may properly insist that they should be washed in clean water; and certainly one should avoid eating this kind of food when it has stood even for a few hours at summer heat in the form of broth.

The *treatment* of cases of mussel poisoning may be stated in a general way. Any and all of the food remaining in the alimentary canal should be removed as far as is possible. Emetics and cathartics are generally recommended, but the stomach tube and irrigation of the intestines are more prompt, efficient, and reliable. The action of the heart should be watched, and strychnine, aromatic spirit of ammonia, or other stimulants may be administered hypodermatically. It is true here, as it is of other forms of food poisoning, that those patients who are least successful in getting rid of the materies peccans by nature's efforts, as manifested in vomiting and purging, are often the ones who are in greatest danger.

Fish Poisoning (Ichthyotoxismus).

Fish poisoning admits of discussion under two distinct categories. In one of these the poison is a physiological product of the activity of certain glands of the animal. The intervention of bacteria is not necessary to render the secretion of the glands active. In fact, there is no bacterial infection. In the second form the flesh owes its poisonous properties to the products of bacterial growth.

Blanchard has proposed that the Spanish word siguatera (pronounced sig-wah-té-ra) be employed to cover those cases due to the action of poisons physiologically formed within the animal. His statement is as follows:

"I wish to state that there are two distinct categories of intoxication due to the eating of the flesh of vertebrates.

"1. Botulismus is an intoxication induced by meat inoculated with microbes and containing the ptomaïns elaborated by them. This term is applicable not only to disease caused by market meat, but also to that induced by preserved foods.

"2. Siguatera is an intoxication caused by fresh food, not infected with bacteria, and in which the poisonous principles are leucomaïns formed by the physiological activity of the tissue. I propose to designate this category of intoxication by the word siguatera, a name employed by the Spanish physicians of the Antilles to indicate poisoning from the eating of fish."

While I have not accepted Blanchard's nomenclature as applicable to all kinds of poisonous meats, the distinction made by him in the above quotation admirably states the differences in the two kinds of fish poisoning. It is a question whether or not I should mention those fish whose flesh is not harmful, but which are supplied with poisonous glands. However, as the secretions of the special glands owe their toxic properties to physiological poisons, I will include them in the category, but will make my mention of them short.

Some fish are supplied with poison glands connected with tubular barbs, and by means of these they protect themselves. *Trachinus draco*, ordinarily known as the "dragon weaver" or "sea weaver," is one of the best known of these fish. The varieties of this species are widely distributed in salt waters. It is a handsome fish, somewhat resembling the trout, and marked with blue and brown stripes. Dunbar-Brunton describes its poison apparatus as follows: "Upon each of its gill-covers there is situated the spine in connection with the special gland. This spine is grooved and slightly erectile, and is attached partly to the maxilla and partly to the under surface of

the gill-cover. It passes through the gill-cover where it shows as a sharp point, in lengths varying with the size of the fish. The spine is covered with a very fine membrane almost to its free extremity, and this membrane converts the grooves on the spines into little canals, which open near the extremity of the spine. At the base of the spine upon the upper surface lies the poison gland, under the gill-cover and partly covered by the adductor muscle of the gill-cover, which helps to compress the gland, forcing the fluid into the canals, and at the same time erects the spine. When the spine enters another fish or another animal, its membrane is stripped back, and the poison enters at once into the wound. The gland is small, with nucleated colorless cells, secreting a transparent fluid."

While bathing, men sometimes wound their feet with the barbs of this fish, which lies half buried in the sand. It also happens that fishermen sometimes incautiously prick their fingers with the barbs. Almost immediately knife-like pains are felt about the wound and quickly extend over the body. Cardialgia may be most excruciating. There is a sensation of suffocation. The forehead is covered with a profuse, cold perspiration. The heart becomes weak, and beats intermittently. Pain and terror combine and render the condition agonizing to the attendant. Convulsions with wild delirium come on, and finally death, apparently from exhaustion, supervenes. This is the history of a severe case. Ordinarily the symptoms are less grave, and severe local pains accompanied by œdema and followed by gangrene is the usual result.

Some experiments with this poison have been made on the lower animals, especially on rabbits and guinea-pigs. If the thigh of one of these animals be pierced with a barb of the fish, there is a cry of pain and soon the limb begins to twitch. The whole body may be involved in convulsive movements, which resemble those due to strychnine, inasmuch as they are intensified by touching the animal. Respiration usually becomes difficult, and paralysis of the posterior extremities often results. Death may occur within one hour after the infliction of the wound.

There has been no successful study of the chemistry of this secretion. It is claimed by some, and denied by others, that the poison is formed only during the spawning season.

The treatment of wounds from these barbs should be prompt and radical. A deep crucial incision should be made at the point of puncture, and free hemorrhage encouraged. Then the wound should be cauterized. Alcohol, coffee, ammonia, strychnine, whichever is at hand, should be administered.

In *synanceia brachio* there are in the dorsal fin thirteen barbs, each

connected with two poison reservoirs supplied from tubular glands. The secretion from these glands is clear, bluish, feebly acid, and when introduced beneath the skin it causes local gangrene, and, if in sufficient quantity, general paralysis.

In *plotosus lineatus* there is a single tubular barb in front of the ventral fin, and the poison is not discharged unless the end of the barb is broken. The intensity of the poison varies greatly in the different species of this family, being greatest in those living in tropical waters.

In *scorpæna scrofa* and other species of this family there are open poison glands, connected with the barbs in the dorsal and in some varieties in the caudal fin.

In *murœna helena* there is a pocket on the gums or in the roof of the mouth, the walls of which are lined with poisonous glands, the secretions of which moisten the teeth and thus render the bite of this fish poisonous.

In *thalassophryne*, a genus of batrachian, there is a half-closed poison gland on the gill-cover and another on the back. There is no muscular arrangement for the ejaculation of the poison, which is contained in loose bags beneath the skin carrying the barbs.

Kakké was at one time a very prevalent disease in Japan and other countries along the eastern coast of Asia. Many theories were advanced to account for its etiology. Some of them were quite naturally founded upon the superstitions of that part of the world. However, with the opening up of Japan to the civilized world, the study of this disease by scientific methods was undertaken by foreign physicians and by the observant and intelligent natives who acquired their medical training in Europe and America. It was soon noticed that the disease was confined to the seacoast districts, and particularly to the natives, Americans and Europeans living in Japan being almost wholly exempt. With improved transportation, kakké was found to extend towards the interior of Japan. Among the natives the most robust seemed to be most prone to the disease. With these observations the following additional facts were recognized: (1) The inhabitants of the coast were formerly the only natives who partook largely of seafish; (2) improved transportation carried these food products towards the interior; (3) the foreigners did not consume these fish so largely as the natives did; (4) among the natives the most robust would quite naturally eat more food of any and all kinds than the less vigorous.

The above-mentioned observations led Miura to define the disease as follows: "Kakké is a chronic or subacute, seldom an acute, intoxication, due to the consumption of certain kinds of fish." He then

set himself to solve the questions: (1) What fish are the bearers of the poison? (2) In what conditions are these fish poisonous? In Tokio the disease generally appears in May, reaches its greatest prevalence in August, and gradually disappears in September and October. This would indicate that if the disease was due to the eating of fish, the poisonous species must be those that were in demand from May to September. Six species were found to be most abundantly, in fact almost exclusively, used at this time of the year, and all of these belonged to the family of *Scombridæ*. This is in accord with the observation of Gubarew, who had previously reported cases of poisoning from eating scomber saba. However, the etiological relation of these fish to kakké cannot be said to be positively established. It is true that in some parts of the world certain species of scombridæ are eaten without injurious effects. Nothing definitely is known about the nature of the poison in these fish, nor has it been determined whether the active agent is a physiological product of certain glands or a result of bacterial activity. Kakké is a non-febrile disease, the most characteristic symptoms of which are disturbances of the heart's action and dyspnœa consequent upon paralysis of the diaphragm, according to Miura. The same authority claims that electrical stimulation of the diaphragm has proven the most successful treatment.

There are other kinds of fish in Japanese waters that undoubtedly are poisonous. These belong to the *Tetrodon* (Fugu), of which, according to Remy, there are twelve species whose ovaries are poisonous. In winter, when the ovaries are atrophied, they are least poisonous. However, Remy reports the following experiments made with fish caught in the winter:

Dogs fed upon the ovaries or testicles soon sickened, with salivation, severe and frequent vomiting, and convulsive muscular contractions. Soon after the poison was removed from the stomach by vomiting, recovery followed. In order to prevent this rapid elimination, these organs were rubbed up in a mortar and the fluid portion was administered subcutaneously. By this method, notwithstanding the fact that the experiments were made in the winter, death followed in less than two hours. The symptoms consisted mainly of disturbances of the digestive and nervous systems. The most constant were uneasiness, salivation, vomiting of much mucus, severe contraction of the abdomen, then paralytic symptoms, relaxation of the sphincters, marked dyspnœa, cyanosis, and dilatation of the pupils. Death was due to dyspnœa. On section, the salivary glands and pancreas were found injected and ecchymosed. There were small hemorrhagic spots in the stomach and intestines. The liver and kidneys were

filled with dark blood, as is seen in death from asphyxiation. No structural changes could be found in the nervous system.

Miura and Takesaki have studied this poison in tetrodon rubripes. They find the active agent present only in the female sexual organs. The following will illustrate the effects of this poison as observed by these investigators:

To a rabbit of average size there was administered subcutaneously 2 c.c. of an extract from the ovary. Within about twenty-five minutes the respiration became deep and labored, the pupils were dilated and reactionless. After a few severe convulsions the animal fell upon its side and became comatose. Passive movements did not meet with any resistance. The ears were at first engorged and then pale. Thirty minutes after the injection respiration ceased, but at this time the increased peristaltic movement of the intestines could be observed through the walls. The thorax and abdomen were opened. Not a drop of blood flowed from the wound. The heart was still beating. The ventricular beat was 20, and the auricular was 110 per minute. In two and one-quarter hours after the injection the ventricular beat ceased in systole, and a few minutes later the auricles stopped, filled with blood. Rigor mortis set in before the heart ceased to beat; the liver, spleen, and kidneys were filled with blood.

Tahara reports that he has isolated from the roe of the tetrodon two poisons. One of these is a crystalline base, to which he has given the name tetrodonin; while the other is a white, waxy body, and is designated as tetrodonic acid. While both are markedly poisonous, the acid is more active than the base.

The most marked symptoms observed in man poisoned with fugu are referable to the nervous system, although vomiting may be severe and hemorrhage from the stomach may occur. Of 933 cases reported in Tokio from 1885 to 1892 inclusive, 680 were fatal—a mortality of more than 72 per cent.

The fish poisoning so frequently observed in the West Indies is believed to be due to the fact that the fish feed upon decomposing medusæ, corals, and like material. It is stated that all the fish caught off certain coral reefs are unfit for food. *Clupea thirissa* and *clupea venenosa*, also certain species of *scarus*, are found among these. It is possible that the fish become infected from their food and transmit this infection to man. However, all statements concerning the origin and nature of the poison in this class of fish are mere assumptions. No scientific work has been done with them. The poison, whatever its origin may be, is quite powerful, and death not infrequently results. The symptoms are those of gastro-intestinal irritation, followed by collapse. The proper treatment

consists of washing out the stomach and intestines, and the hypodermatic injection of strychnine, ammonia, or alcohol.

At this point it might be well to state that the suggestion has been made that fish poisoning might in some cases be due to the substances employed by certain people to kill fish. This is a possibility, but hardly a probability. That it does not explain the majority of cases of fish poisoning is shown by the fact that in some localities where this method of securing fish is practised, ill effects from the fish thus obtained are unknown or are infrequent; while in other countries where fish are not obtained in this manner, fish poisoning is common. The vegetable substances employed by semicivilized peoples to benumb or kill fish are quite numerous. Cocculus indicus has been used for this purpose. Piscidia, or Jamaica dogwood, owes its scientific name to the fact that it has long been used in the West Indies to benumb fish. The leaves and entire branches are thrown into the water. In some places the bark of the root is also used. The active principle, called piscidin, consists of white prisms, and is believed to have the formula $C_{29}H_{24}O_7$. It seems to have a paralytic action on the motor centres, and the fish, being unable to swim on account of this action, float on the surface and in this benumbed condition are gathered in. While the substance is poisonous to man, much larger amounts than would occur in the fish taken at a single meal would be necessary in order to induce any effect. Moreover, the symptoms of West Indian fish poisoning are wholly different from those caused by dogwood. Pachyrrhizus angulatus and derris elliptica are employed in the Dutch East Indies in securing fish, and an extract of derris root is said to be employed in Borneo as an arrow poison. Both of these plants contain non-nitrogenous substances that are highly poisonous to fish and relatively harmless to other animals. It is stated that the extract of derris root kills fish when mixed with water in the proportion of 1:25,000, and its active principle in a dilution of 1:5,000,000. Greshof has isolated both of these substances, and named one derrid and the other pachyrrhizid. Yet the underground stems of pachyrrhizus angulatus, the "yaka" of the Fijians, are used by man as a food; and in Cochin China derris root is an ingredient of a chewing gum known as "betel." The leguminous plant, Tephrosia ichthyonecea s. toxicaria, the indigo plant of the Niger River, which has been transplanted to the West Indies, furnishes leaves and branches that are used in killing fish, while its roots are employed medicinally in the treatment of skin diseases. However, in large doses the active agent of this plant is poisonous to man. The fish poison of Java, from Milletia atropurpura, contains the glucoside saponin, $C_{32}H_{54}O_{16}$, which is found in various

other plants. The active agent in hydrocarpos inebricans, employed in Ceylon in catching fish, is said to be hydrocyanic acid. Robinia nicou is another leguminous tree that furnishes a fish poison. It contains a crystalline substance which kills fish in a dilution of 1:1,000,000. Several species of robinia are also poisonous to man, and the symptoms may be those of a gastrointestinal irritant. Chewing the inner bark of the common locust (R. pseudacacia) has been known to cause most violent vomiting, coldness of the extremities, and stupor. Other fish poisons of the West Indies are jacquinia armillaris, which, on account of the fact that its dried fruit is used for bracelets, is known as *bois bracelet*, and Serjunia lethalis, from which the poisonous honey of a certain wasp is prepared. This honey, even in a small quantity, is said to produce a mild intoxication. This will remind the classical student of the poisonous honey connected with the retreat of the ten thousand Greek soldiers under Xenophon, which occurred four centuries before our era.

Fish may be infected with some pathogenic bacterium, and this or its chemical products may, when taken by man in his food, prove deleterious. Recent studies indicate that this is at least one of the causes of the severe epidemics of fish poisoning frequently observed in Russia. Schmidt concludes his investigations of one of these outbreaks with the following statements:

1. The harmful effects are not due to putrefactive processes.

2. Fish poisoning in Russia is always due to the eating of some member of the sturgeon tribe.

3. The ill effects are not due to the methods of catching the fish, the use of salt, or imperfections in the methods of preservation.

4. The deleterious substance is not uniformly distributed through the fish, but is confined to certain parts.

5. The poisonous portions are not distinguishable from the non-poisonous, either macroscopically or microscopically.

6. When the fish is thoroughly cooked it may be eaten without harm.

7. The poison is an animal alkaloid, produced most probably by bacteria that cause an infectious disease in the fish during life.

Fish poisoning in Russia is sometimes quite fatal, as many as fifty per cent. of those affected dying. Eleven cases with five fatal terminations came under the observation of Arustamov, who found in the fish and in the viscera of the dead persons a germ resembling, but not identical with, the typhoid bacillus. The fish were eaten raw and the ill effects were believed to be due to the above-mentioned bacillus. The symptoms were dryness of the throat, mydriasis, vertigo, general weakness, and dyspnœa.

Sieber obtained the bacillus piscicidus agilis from some fish, the eating of which was followed by disastrous consequences. In this instance the fish were taken from a pond in which as many as thirty dead fish were found in the course of two days, and many others that were quite evidently sick. From both the sick and the dead animals the bacillus was obtained. This germ is anaërobic, forms spores, and grows rapidly on ordinary culture media. It is pathogenic not only to fish, but also to frogs, mice, rabbits, dogs, and guinea-pigs. It is highly toxicogenic, the filtered cultures being quite virulent. From old cultures one poison was obtained by distillation. Cadaverin and other known bases, and at least two poisons of unknown composition, are contained in old cultures. Of one of these substances, 3.5 mgm. sufficed to kill a frog within fifteen minutes. The chief symptoms observable in this animal were apathy, dyspnœa, and paralysis.

Anrep states that there are two active ptomaïns (ichthyotoxins) in poisonous fish. One of them may be extracted from alkaline solutions by chloroform, benzin, or ether. This is an amorphous substance, insoluble in water, but capable of forming soluble salts. One-fourth of a milligram of the hydrochloride induces marked effects in dogs, and twice this quantity kills rabbits. The second base is an oily substance and less energetic in action. In 1889 Jakolev obtained from poisonous sturgeon a base similar to but not identical with the first of Anrep's bodies. All of these poisons have a paralyzing action on frogs, dogs, and rabbits, arresting respiration and the action of the heart. In cats they cause continued convulsions. The more active of Anrep's bases, for which he proposes the name halichthyotoxin, dilates the pupil on local application. The base is destroyed at the temperature of boiling water, and it has been frequently observed in Russia that those who eat raw fish are seriously affected, while those who partake of the same food thoroughly cooked escape.

There is some difference of opinion concerning the causation of the so-called "Barben cholera," frequently observed in certain districts of Germany. Some hold that the barbels, the eating of which is followed by disastrous consequences, are sick with some infectious disease; while others believe that the poison originates in putrefactive changes. The symptoms are those of cholera nostras. The proper treatment consists of washing out the stomach and intestines, and a hypodermatic administration of heart stimulants, if this be indicated by marked depression. The employment of opiates is to be condemned.

In the United States the cases of ichthyotoxismus most frequently seen are due to infection of this food with saprophytic, toxicogenic

bacteria. When the effects are confined to an irritation of the stomach and bowels, as evidenced by nausea, vomiting, and purging, the condition is designated ichthyotoxismus gastricus. When the digestive disturbances are accompanied by a rash, it is known as ichthyotoxismus exanthematicus. The writer has seen several cases of both of these varieties caused by the eating of canned salmon. In all the vomiting has been persistent and exhaustive. In some there has been purging, but in the more dangerous cases the bowels have been constipated. There is probably in all in the first stages of the poisoning some elevation of temperature, sometimes as high as 102° F. When proper treatment is begun early enough, the chances of recovery are good. Nature's efforts to remove the poison should be assisted by the stomach tube and irrigation of the colon. In adults it is well to administer ten grains of calomel after the stomach has been well cleansed, for the purpose of emptying the small intestines. In one of the cases referred to large doses of morphine had been administered early in order to check the vomiting and purging, and in this case death resulted. The danger of thus arresting the elimination of the poison cannot be too emphatically condemned.

Dilatation of the pupils is frequently observed in fish poisoning, as well as that due to the consumption of other decomposed food. The substance which induces this reaction is known as ptomatropin (cadaveric atropine), and may be removed from alkaline solution by agitation with ether. However, this substance has never been obtained in a pure state, and we know nothing of its composition. Its presence can be recognized only by the application of the extract to the eye. It may be well in this connection to call attention to the undesirability of depending upon this effect on the pupil in the test for atropine in toxicological examinations. The writer was once called upon in a medico-legal case, in which the chemist, after having examined a body that had been buried for some weeks, testified that the stomach contained four grains of the sulphate of atropine, because he obtained an extract from the stomach, and this extract dissolved in an ounce of water had about the same effect on the pupil of a cat's eye that would be induced by a solution of four grains of atropine sulphate in the same volume of water. After hearing the opinion of two other chemists on the value of this test, the judge very properly decided to discontinue the case. This extract from decomposing animal tissue resembles atropine not only in dilating the pupil, but in other effects as well. It causes dryness and constriction of the throat, ptosis, paralysis of the accommodation, weak and rapid pulse, nervous excitement, possibly convulsions, and delirium, passing into coma. It has been suggested that a ptomatropin may be formed in

the body in typhoid fever, and this may account for the delirium so frequently observed in this disease. However, this is only an assumption. After death from the so-called ptomatropin, section shows congestion of the brain, lungs, and kidneys, often hemorrhagic spots in the stomach and intestines, and cloudy swelling of the solitary follicles and Peyer's patches. According to the statement of Schmidt, 100 gm. of putrid sturgeon yield 3 mgm. of ptomatropin, a quantity sufficient to kill two men.

The explanation of the fact that canned fish is sometimes poisonous is probably to be found in incomplete sterilization in the canning. The bacteria are not all killed, and grow under anaërobic conditions, elaborating a potent poison. One such can, the contents of which had previously affected those who partook of it, was examined both chemically and bacteriologically by the writer. The absence of metallic poisons was demonstrated. The only microorganism that could be found was a micrococcus, and animals inoculated with this remained unaffected; but when this germ was grown for some weeks in sterilized eggs, the contents of the eggs became highly poisonous, while the control eggs remained free from poison.

Meat Poisoning (Kreotoxismus).

It has long been an observed fact that the flesh of animals dead from certain diseases or slaughtered while suffering from these diseases is not a safe food for man. The Mosaic law forbade the eating of the flesh of animals dead from disease. "Ye shall not eat of anything that dieth of itself; thou shalt give it unto the stranger that is in thy gates, that he may eat of it; or thou mayest sell it unto an alien; for thou art a holy people unto the Lord thy God. Thou shalt not seethe a kid in his mother's milk" (Deut. xiv. 21). The first part of this command is certainly wise counsel, but the feeding of a visitor with such food would not now be regarded as in accord with the rules of hospitable entertainment, and the sale of it even to an alien would not be permitted by the law of any Christian country.

The most common diseases that may be transmitted from the lower animals to man by the consumption of the flesh or milk of the former as food by the latter are tuberculosis, anthrax, symptomatic anthrax, pleuropneumonia, puerperal fever, malignant œdema, glanders, various septicæmias, trichinosis, mucous diarrhœa, and actinomycosis. It hardly comes within the scope of this article to discuss in any detail the transmission of these diseases from the lower animals. This is done in the special articles devoted to these diseases in these volumes.

I shall limit the subject of kreotoxismus to those untoward effects due to the eating of flesh invaded by non-specific, toxicogenic bacteria. I must, however, be allowed to offer a few opinions parenthetically concerning a few mooted questions pertaining to the consumption of the flesh of animals affected with a few of the above-mentioned diseases. There has been some variety of opinion among sanitarians concerning the danger of eating the muscles of animals with tuberculosis. These differences have not been confined to opinions, but have appeared in the results of scientific experimentations. There are those who hold that it is sufficient to condemn the diseased part of a tuberculous cow, and that the remainder may be eaten with perfect safety. These believe that tuberculosis is a local affection, that the bacillus is never found in the blood, and consequently is not generally distributed. On the other hand, there are those who teach that tuberculosis is a disease *totius substantiæ*, and that "total seizure" and destruction of the entire carcass by the health authorities are desirable. Inoculation of guinea-pigs with the meat and meat juices of tuberculous animals has given different results to the several investigators. To any one who has seen tuberculous animals slaughtered, these differences of opinion and in experimental results are easily explainable. In the first place the tuberculous invasion may be confined to a single gland, and this may occur in a portion of the carcass not ordinarily eaten, while on the other hand the invasion may be much more extensive and even the muscles may be involved. Again, the tuberculous portion may consist of hard nodules that do not break down and contaminate other tissues in the process of removal, but I have seen a tuberculous abscess in the liver, holding nearly a pint of broken-down infected matter, ruptured or cut in removing this organ and its contents spread over the greater part of the carcass. This easily shows why one investigator succeeds in inducing tuberculosis in guinea-pigs by introducing small bits of meat from a tuberculous cow into the abdominal cavity, while another equally skilful bacteriologist follows these same details and fails to get any positive results. No one desires to eat any portion of a tuberculous animal, and the only safety lies in "total seizure" and destruction. It is an interesting historical fact that the sale of the flesh of tuberculous animals was once forbidden on the belief that the disease was syphilis.

Even a profuse diarrhœa is ordinarily not considered of sufficient importance to prevent the killing of the animal and the consumption of its flesh, but it was such an animal as this whose flesh poisoned a number of persons, as related by Gärtner. This cow had been observed to have a profuse diarrhœa for two days before it was slaughtered. Twelve persons ate this flesh raw, and all of them were affected.

Many of those who ate of the cooked meat were also ill. In the meat and in the spleen of a person who died from eating it, Gärtner found the bacillus enteritidis. Good meat when inoculated with this germ and subsequently cooked for some hours killed rabbits, mice, and guinea-pigs; and boiled bouillon cultures were highly poisonous.

There have been several outbreaks of meat poisoning due to the eating of the flesh of cows slaughtered while suffering from puerperal fever. Fisher reports a case of this kind. This animal was quite seriously ill, and in consequence had lost greatly in weight. Nineteen persons partook of the meat, and in all vomiting and purging occurred a few hours after the meal. Boiling for one and one-half hours did not destroy the chemical poison.

Basenau obtained the bacillus bovis morbificans from the flesh of a cow that was sick at the time of being slaughtered and had calved eight days before. It was estimated that 1 gm. of this meat contained 187,500 bacilli. This germ is pathogenic to mice, rats, guinea-pigs, rabbits, and calves. A bouillon culture was injected into the uterus of a guinea-pig a few hours after she had given birth to three young. Death of the mother, and of the young from taking of the infected milk, resulted. The germ was found in the milk, blood, muscles, liver, and spleen.

Di Mattei claims that the flesh of animals dead of symptomatic anthrax may retain its infection after having been preserved in a dry state for ten years.

We now turn to those cases of true kreotoxismus in which the kreotoxicons result from the growth of non-specific, saprophytic microorganisms. It has long been known that certain putrefactive changes in meat may be accompanied by the elaboration of poison. Panum's pioneer experiments were made with this kind of material. He was the first to establish the chemical nature of this poison, inasmuch as he demonstrated that the aqueous extracts of putrid meat retained its poisonous properties after treatment which would insure the destruction of all organisms, although at that time the existence of fermentative bacteria could hardly be said to have been established. Panum's conclusions were as follows:

1. "The putrid poison contained in decomposed flesh, and which may be obtained by extraction with distilled water and repeated filtration, is not volatile, but fixed.

2. "The putrid poison is not destroyed by boiling. Indeed, it preserves its poisonous properties even after the boiling has been continued for eleven hours, and after the evaporation has been carried to complete desiccation at 100° C.

3. "The putrid poison is insoluble in absolute alcohol, but is

soluble in water, and is contained in the aqueous extract which is formed by treating with distilled water the putrid material which has previously been dried by heat and washed with alcohol.

4. "The albuminoid substances which frequently are found in putrid fluids are not in themselves poisonous, only so far as they contain the putrid poison fixed and condensed upon their surfaces, from which it can be removed by repeated and careful washing.

5. "The intensity of the putrid poison is comparable to that of the venom of serpents, of curare, and of certain vegetable alkaloids, inasmuch as 12 mgm. of the poison obtained by extracting with distilled water putrid material, which had been previously boiled for a long time, dried at 100° C., and submitted to the action of absolute alcohol, was sufficient to almost kill a small dog."

Panum made intravenous injections of this poison, and observed that the effects differed with the quantity of the material and the size and strength of the animal. With large doses death followed quickly. In these instances there were violent cramps and involuntary evacuation of urine and fæces; the respirations were labored, the pallor was marked, sometimes followed by cyanosis, the pulse became feeble, the pupils were widely dilated, and the eyes were projecting. Autopsy revealed no lesion, but the blood was dark, imperfectly coagulated, and slightly infiltrated through the tissue. He also obtained from putrid flesh a narcotic body which was separable from the "putrid poison" by the solubility of the former in alcohol. When the alcoholic solution was evaporated to dryness, the residue taken up in water, and injected into the jugular vein of a dog, this animal fell into a deep sleep that remained unbroken for twenty-four hours, and from which it awoke in apparently perfect health.

The above-mentioned observations were made by Panum in 1856. In 1868 Bergmann and Schmiedeberg obtained first from decomposed yeast and later from putrid blood a poisonous substance which they called sepsin. Small doses (0.01 gm.) of this substance dissolved in water and injected intravenously in dogs caused vomiting and diarrhœa. Autopsy showed ecchymoses in the stomach and intestines. These investigators believed at the time that they had isolated the putrid poison of Panum, but further studies have failed to confirm this belief. Recently Levy, working under Schmiedeberg's directions, has made an additional study of putrid yeast, in which he found bacilli resembling those of mouse septicæmia and the proteus vulgaris. From cultures of these germs the poison was precipitated with absolute alcohol, and this precipitate dissolved in water and intravenously injected into dogs induced the symptoms of sepsin. Levy also found the proteus in some meat

which had poisoned a family. In the vomited matter, in the stools, and in the bottom of the box in which the meat was kept, he found the proteus. He concludes that this bacillus generates sepsin. If this be true the crystals obtained by Bergmann and Schmiedeberg did not constitute the poison. This is highly probable. The effect might have been due to an albuminous body mixed with the crystals.

One of the most frequently observed forms of kreotoxismus is *sausage poisoning*, known as botulismus and alantiasis. This has been frequently seen in parts of Germany. It is undoubtedly due to the method of preparing this article of diet in that country. It was formerly the custom of the peasants of Würtemberg to fill the stomachs of hogs with blood and chopped meat, and these great sausages, called "blunzen," were hung in the chimney to be cured. They frequently froze during the night and thawed during the day. At no time was the temperature high enough to destroy the bacteria in the interior of these sacs. The contents were eaten without being cooked and frequently induced most disastrous consequences.

Some Germans have brought to the United States modifications of the above-described method of preparing sausage, and the writer is at this present time investigating an outbreak in which six persons were poisoned, four of them fatally. In this case the sausage meat was placed in links of intestines, and alternately frozen and thawed and eaten raw.

The fatality in sausage poisoning varies greatly in different outbreaks. In 1820 Kerner collected reports of 76 cases, with 37 deaths. Two years later he had increased the number of cases to 155 and the deaths to 84. In some instances, however, the mortality is low. In an outbreak reported by Müller less than 2 per cent. died.

The symptoms of botulismus vary widely. Indeed, this is true in all forms of bromatotoxismus. The germs that elaborate the chemical poisons are by no means identical, and consequently the poisons formed are not the same. As a rule, there are in sausage poisoning dryness of the mouth, constriction of the fauces, nausea, vomiting, purging, vertigo, dilation of the pupils, and a sense of suffocation. Nervous prostration and marked muscular weakness are often prominent symptoms in those who ultimately recover. In fatal cases the pulse becomes weak and cyanosis is well marked. The surface grows cold and is covered with perspiration. The temperature, which is at first above the normal and may reach 103° F. or even higher, rapidly declines and falls below the normal. Consciousness is usually retained until the last stages, when delirium followed by coma and death results. In some instances disturbances of vision

are early and persistent. At first the patient feels that there is a film before the eyes and tries to break it away, then he goes to the window in order to get a better light. Later everything seems enveloped in a cloud and small objects are wholly invisible. The letters and words on a printed page cannot be seen. In cases of recovery this dimness of vision may persist for two weeks or longer. In the most dangerous cases there is obstinate constipation, usually after a few hours of frequent watery stools, although there may be no diarrhœa at all and the attendant may find the administration of cathartics to be without effect.

Autopsy shows no constant or characteristic lesion. Hyperæmia of the mucous membrane of the stomach and intestines has been observed but is by no means universal. Occasionally there are hemorrhagic spots in the alimentary canal. The abdominal and thoracic viscera, as well as the brain, have been found engorged with blood, but this is due to failure of the heart, and is not at all characteristic of sausage poisoning. Some have placed considerable stress on the observation that putrefaction is unusually delayed, but Müller has shown that no reliance can be placed upon this statement, and he says that in forty-eight recorded autopsies it was noted that in eleven putrefaction rapidly developed.

All kinds of theories concerning the nature of the poison have been advanced. For a long while it was believed to be a special fatty acid, to which the name "acidum botulinicum" was applied, but later researches demonstrated that the supposed special acid has no existence, and that the fats actually present are harmless. It was once suggested that the harmful ingredients consisted of pyroligneous acid absorbed from the smoke, but then it was ascertained that sausage that had never been smoked might be highly poisonous. Hydrocyanic and picric acid have been mentioned, but how these could possibly find their way into the meat is more than any one can tell. Moreover, the symptoms are altogether at variance with this suggestion. Attempts to isolate the kreotoxicons have all so far failed.

Instances of poisoning with meats from various animals and from nearly every part of the animal ordinarily used as food have been observed and reported. Ballard believed that an epidemic of pneumonia at Middlesborough, England, in 1888, was due to infected meat. This epidemic resulted in four hundred and ninety deaths among the iron workers of this district. Bacon was believed to be the bearer of the infection. Out of twenty samples of this meat examined, fourteen were distinctly poisonous to rats and other rodents fed with it. Two other samples seemed to affect the animals, but did not cause death, and only four proved to be wholly without

effect. The same germ was found in the animal and in the people dead from the disease. Moreover, the lesions were very similar in the men and the animals. The microorganisms were neither the bacillus of Friedländer nor the diplococcus of Fraenkel and Weichselbaum. The disease was regarded as one *sui generis*. The writer once observed a small number of cases of septic pneumonia which, there were good reasons for believing, were due to infection from food, but as the articles eaten at a meal partaken of by all the sick had been destroyed, no satisfactory investigation could be made.

Of two hundred men at a banquet at Sturgis, Michigan, April 26th, 1894, every one who ate of the pressed chicken served was made ill. Some who were not at the dinner, but who aided in preparing it, took small bits of the chicken, and these were also sick. All were attacked, within from two to four hours after eating the chicken, with nausea, violent griping, and purging; many fainted while attempting to arise from bed. The chickens were killed Tuesday afternoon and left hanging in a market room at ordinary temperature until Wednesday forenoon, when they were drawn and carried to a restaurant, and here left in a warm room until Thursday, when they were cooked (not thoroughly), pressed, and served at the banquet that night. The chickens contained two germs, a slender bacillus and a streptococcus. The former was fatal to white rats, guinea-pigs, and rabbits, when inoculated intraperitoneally, intravenously, and subcutaneously. Instances similar to this might be multiplied.

Ermengem obtained from ham and from the spleen of a person who had eaten this meat, a germ to which he has given the name bacillus botulinus. Cats, rabbits, guinea-pigs, and apes are susceptible to this germ when taken by the mouth. The most prominent symptoms observed were marked and persistent mydriasis, increased flow of the pharyngeal and bronchial secretions, and various partial pareses, among which may be mentioned prolapse of the tongue, aphonia, aphagia, croupy cough, and retention of the urine, fæces, and bile. The bacillus botulinus is an obligate anaërobe and elaborates a powerful toxin which has not as yet been isolated.

Cases of poisoning from the eating of canned meats have become quite common. Although it may be possible that in some instances the untoward effects result from metallic poisoning, in the great majority of instances the poisonous agents are formed by putrefactive changes. In one instance reported by Ungefug and confirmed by the great chemist, Heinrich Rose, sulphate of zinc had been used as a preservative instead of saltpetre. This must, however, be regarded as exceptional. In many cases it is probable that decomposition begins after the can has been opened by the consumer; in others

the canning is imperfectly done and putrefaction is far advanced before the food reaches the consumer. In still other instances the meat may have been taken from diseased animals, or it may have undergone putrefactive changes before the canning.

Ermengem states that since 1867 there have been reported in medical literature one hundred and twelve epidemics of meat poisoning, in which six thousand persons have been affected. In one hundred and three of these outbreaks the meat came from diseased animals, while in only five was there any evidence that putrefactive changes in the meat had taken place.

The treatment of kreotoxismus should consist in aiding the removal of the harmful substance from the body, washing out the stomach and intestines, the adminstration of intestinal disinfectants, and the maintenance of the heart's action.

Milk Poisoning (Galactotoxismus).

The term galactotoxismus is here employed to indicate the harmful effects that may result from the drinking of milk infected with saprophytic, toxicogenic bacteria. This excludes all discussion of the distribution of the specific infectious diseases through milk as a carrier of the infection. The transmission of the infectious diseases, such as tuberculosis and septic fever, from the lower animals to man by the use of the milk of the former as a food by the latter, is also a subject that will not be discussed in this connection.

It is certainly true that infants are much more susceptible to the action of the galactotoxicons than are adults. Neither can there longer be any doubt that these poisons are largely responsible for a large percentage of the infantile mortality, which must be admitted to be alarmingly high in all parts of the world. That the summer diarrhœa of infancy is due to milk poisoning has been quite positively demonstrated. These diarrhœas are not due to a specific microorganism, but there are many bacteria that grow readily in milk and elaborate poisons that induce vomiting and purging and may cause death. These diseases are found almost exclusively among children that are artificially fed. There are differences in chemical composition between the milk of woman and that of the cow, but these variations in percentage of proteids, fats, and carbohydrates are of less importance than the infection of milk with harmful bacteria. The child that takes its food exclusively from the breast of a healthy mother obtains a food that is free from poisonous bacteria, while the bottle-fed child may take into its body with its food a great number and variety of bacteria, some of which may be quite deadly

in their effects. The diarrhœas of infancy are practically confined to the hot months, because a high temperature is essential to the growth and wide distribution of the poison-producing bacteria. Moreover, decomposing matter may harbor and support these bacteria at a time when the outdoor temperature is high enough to allow of their growth. The emphatic way in which attention has been called within recent years to the danger of infected milk has led to marked improvement in the handling of this article of diet, but that there is yet room for improvement in this direction must be granted. The sterilization and pasteurization of milk have doubtlessly saved the lives of many children, but it remains a fact that the most intelligent often fail to secure milk that is altogether safe.

Flügge has made a most valuable contribution to our knowledge of the bacteria in milk that may elaborate poisons and induce the symptoms observed in the summer diarrhœas of infancy. He finds in milk four anaërobic bacteria and two of these may produce poisons. A milk culture of one of these was passed through a Berkefeld filter and injected subcutaneously in mice in amounts of from 0.3 to 0.6 c.c. The mice died after from three to fifteen hours. Section showed distinct hyperæmia of the intestines and the presence of transudates in the peritoneal and pleural cavities. Larger doses (5 c.c.), given intraabdominally, killed guinea-pigs within from fifteen to twenty hours. These bacilli cannot be considered harmless, and it is worthy of note that they grow much better at from 30° to 37° C. than they do below 22° C. Some of the anaërobic bacteria produce a disagreeable odor in milk and this would probably prevent an adult from drinking it, but it might be disregarded by a hungry infant.

Flügge's most interesting results were obtained by the study of the peptonizing bacteria in milk. Twelve species of this kind were isolated and studied. Milk infected with peptonizing bacteria develops the bitter, irritating, characteristic taste of peptones, but this would not be observable during the first few days of the growth and it is at this time that it would be taken by children. Indeed, a sample of milk may contain millions of peptonizing bacteria and still be sufficiently agreeable to the taste to be readily taken. These bacteria grow rapidly at a temperature as high as 44° C., and their spores resist a temperature of 100° C. maintained for two hours. This demonstrates the fact that these bacteria escape ordinary sterilization. Moreover, the necessity of keeping the milk fed to children at a low temperature is shown by the observation that these germs fail to multiply except when the temperature is high. Sterilization may destroy the developed bacilli, while the spores remain possessed of vitality, but fail to develop if kept at a low temperature. Of the

twelve peptonizing bacteria isolated by Flügge, nine failed to develop any poison. Therefore any harmful effects attributable to them must be due to the peptones. It is interesting to note in this connection that it is by no means certain that it is well to feed children upon milk peptonized by the agency of bacteria or by means of the digestive ferments. In testing the nutritive value of peptones on the lower animals and on both healthy and sick men, severe intestinal irritation has been induced. Züntz found that dogs fed upon peptones suffered from an abundant watery diarrhœa and eliminated from three to six times as much unused nitrogen as those fed upon meat. Pfeiffer caused in himself and in another man intestinal irritation and diarrhœa by large doses of peptones. Neumeister states: "By long-continued use of these preparations symptoms of marked irritation and injury to the intestines uniformly resulted, and consequently the prescription of albumoses in disease can scarcely be regarded as rational."

With the three other peptonizing bacteria from milk Flügge obtained positive results. Cultures of No. I., two days old, injected in quantities of 2 c.c. into the dorsal lymph sacs of frogs caused at first slowness of motion, and loss of reflex, after one hour paralysis of the extremities, and after four hours death. In doses of 0.5 c.c., subcutaneous injections killed mice after from five to six hours. With the exception of the absence of voluntary movements and tardiness of reaction, no symptoms were manifested by these animals. Five cubic centimetres given intraabdominally to guinea-pigs caused marked dyspnœa and death after from four to seven hours. In these animals the abdomen was retracted, and handling them evidently caused pain. Section showed hyperæmia of the peritoneum, serous coat of the intestines, and kidneys. Dogs drank with apparent relish large quantities of milk culture of this bacillus, but about one hour later severe diarrhœa set in with a discharge every few minutes.

Milk cultures of No. III. were without effect on frogs and mice, but caused sharp diarrhœa accompanied by a severe abdominal pain in puppies when administered by the mouth: "One of the puppies showed on the second day progressive exhaustion, paralytic weakness of the extremities, and a fall in the temperature. He died on the third day. Section showed hyperæmia of the kidneys; nothing else worthy of note."

"Bacillus No. VII. injected in milk culture into frogs, mice, and guinea-pigs had no marked action. When the culture was filtered through a Chamberland bougie and concentrated in vacuo to one-fifth its volume, it killed mice and guinea-pigs in doses of 0.6 and 5 c.c. respectively. Death, which followed in from six to twelve hours, was

preceded by dyspnœa and convulsive movements. Section showed nothing characteristic. Even the unconcentrated milk cultures acted powerfully when fed to puppies. After feeding for one or two days profuse diarrhœa set in, but disappeared the next day (the feeding being discontinued). The diarrhœa was accompanied by great emaciation, weakness of the extremities, and tottering gait. As soon as the use of the culture was discontinued, and ordinary milk given, improvement began and continued until complete recovery. Two puppies after recovery were again fed with the culture. After a short time the profuse diarrhœa with its accompanying symptoms reappeared."

Flügge concludes that the effects of these cultures cannot be due to the peptone, or, if so, they must elaborate special peptones. The symptoms and the post-mortem findings are not those of peptone poisoning. Moreover, the bacillus that forms the least amount of peptone yielded the most virulent cultures. In market milk Flügge found these poisonous, peptonizing bacteria frequently present in pure cultures.

Lübbert has continued Flügge's work on the peptonizing bacteria of milk. He states that they are widely distributed, being found in hay, in the soil, and in the fæces of cows. They do not grow at a temperature below 22° C., and their spores resist 100° C. for two hours. These bacteria act solely upon the proteids of milk, at least during the first twelve days. Lübbert shows this to be true by the following table:

Experiment.	The sterile milk contains.	Infected and kept at 37° for one day.	After six days.	After twelve days.
I.....	Fat.....3.000 per cent.	2.999	3.001	2.999
	Proteid..3.330 "	2.133	1.403	0.735
	Sugar....4.289 "	4.2887	4.289	4.289
II.....	Fat.....3.006 "	3.009	3.004	3.000
	Proteid...3.329 "	2.400	1.184	0.874
	Sugar....4.294 "	4.294	4.291	4.294

It will be seen that while the fat and carbohydrate remained undiminished, the amount of proteid was greatly reduced. Caseoses were formed, and some of them could be precipitated by copper sulphate while a portion could be removed from solution by precipitation with ammonium sulphate. Amido-acids were not found. Some of this milk was fed to four guinea-pigs twenty-four hours after inoculation. All of these animals died within four days. Three young puppies fed with the same milk developed severe diarrhœa two hours after taking the milk, and died on the fourth, sixth, and seventh days. Another puppy was fed upon the freshly infected milk and developed

a diarrhœa that continued for three days and then terminated in recovery. A fourth dog, several months older, took the milk freely without any effect, thus showing that age gives immunity to the poison in dogs, as it undoubtedly does in children.

Section of the animals killed with the milk showed only slight swelling and injection of the mucous membrane of the small intestines. The germs were not found outside the intestinal canal, and both subcutaneous and intraabdominal inoculations with small quantities of pure culture were without effect. Two cubic centimetres or more of milk culture twelve hours old or older given intraabdominally caused death. By growing the milk cultures in thin layers with large surface exposure the virulence was so far increased that 1 c.c. given intraabdominally to guinea-pigs caused death. In the animals killed by intraabdominal injections of from 5 to 10 c.c. of milk culture, an intense enteritis was found. The serosa was dark red and dotted with pinhead, hemorrhagic spots. In some instances a small amount of bloody fluid was found in the peritoneal cavity.

Lübbert has found that the cells of these bacteria contain the chemical poison, and when the bacteria are removed from cultures by filtration the filtrate is wholly inert. Moreover, when the bacteria are killed by the action of heat or by exposure to vapor of chloroform, the poisonous constituent is rendered innocuous. It requires from twenty-three to twenty-four millions of these bacteria injected intraabdominally to kill a guinea-pig weighing 300 gm.

The writer has obtained these peptonizing bacteria from the milk taken by a child about two hours before the onset of a severe form of summer diarrhœa, and can confirm the above-mentioned statement from Lübbert. Milk cultures were kept in an incubator from one to forty days, and at no period during this time was the milk after removal of the germs by filtration found to be poisonous. Indeed, with some of these peptonizing bacteria cultures after the fifteenth or sixteenth day contain only dead bacilli, and when this point is reached the unfiltered milk is not poisonous. The peptonizing bacteria with which I have worked are probably not identical with those studied by Flügge and Lübbert, but they belong to the same class.

With these facts before us there can scarcely be a doubt that the peptonizing bacteria of milk constitute an important factor in the causation of the summer diarrhœas of infancy, and that these diseases are cases of galactotoxismus. I will offer a theoretical explanation of the susceptibility of infants to these bacteria, and the immunity of older children and adults to the same. In doing so, I will make the following quotation from an article written by myself in 1888 (*Medical News*, No. 52, 1888, p. 621).

"If it be true, as is stated by Traube and Escherich, that in the young child stomachic digestion is of less importance than intestinal digestion, and that the stomach is more a receptacle into which the milk is received for coagulation than a digestive organ, then we have the most favorable conditions for the growth and activity of the bacteria that are introduced with the food. These experimenters claim that the younger the child the less active is digestion in the stomach, and that in this organ the milk is coagulated and is passed through the pylorus undigested. Hammarsten some years ago showed that this is largely the case in the dog and rabbit. Hoffmeister and Tappeiner find that the stomach does not absorb soluble substances as rapidly as does the mucous membrane of the small intestines; and Zweatfel has stated, and in this he is supported by Hammarsten, that the proteolytic activity of the pancreatic juice is relatively well developed in the newly born. Furthermore, it has been demonstrated by Eichhorst that the intestinal mucous membrane (in the infant) will absorb unchanged casein." I would suggest that the susceptibility of infants to these bacteria is due to the great readiness with which the mucous membrane of the intestines of infants absorbs casein, and that the casein carries along with it the bacterial cells containing the chemical poison. Later in life the stomach becomes of more importance as a digestive organ and absorption through the wall of the intestines is modified.

It must not be inferred that the peptonizing bacteria are the only poisonous germs that find their way into milk, or that adults are immune to every form of galactotoxismus. Neither can it be assumed that other microorganisms may not cause the summer diarrhœas of infancy. Some of these bacteria do elaborate soluble chemical poison. Some years ago the writer found tyrotoxicon in a sample of milk, the drinking of which was followed by a violent form of cholera infantum. Nine years ago, I wrote the following sentence, which has been confirmed by subsequent researches: "The microorganisms which induce the catarrhal or mucous diarrhœas of infancy may be, and probably are, only putrefactive in character, but those which cause the choleriform or serous diarrhœas, true cholera infantum, are more than putrefactive—they are pathogenic; they produce a definite chemical poison the absorption of which is followed by the symptoms of the disease."

In 1890 I studied the chemical products of three of the germs obtained by Booker from the fæces of children with summer diarrhœa. Of these bacteria Booker stated: "X was found almost as a pure culture in the fæces of a fatal case of diarrhœa; *a* was strongly pathogenic when tested last winter. A was isolated last summer;

liquefies gelatin, and belongs to the proteus group." Beef-tea cultures of these germs were kept in the incubator at 37° C. for ten days, and then twice filtered through heavy Swedish filter paper. The second filtrate was allowed to fall into a large volume of absolute alcohol feebly acidified with acetic acid. The precipitates that formed in the alcohol were collected and dried on porous plates, and their action on animals was tested. The precipitate obtained from cultures of X was slightly yellow as seen deposited in alcohol, but became greenish on exposure to the air. It was freely soluble in water, and gave the biuret and xanthoproteic rections. It was precipitated by saturating its aqueous solution with ammonium sulphate, and could not, therefore, be classed among the peptones. Sodium sulphate and carbonic acid failed to precipitate it from aqueous solution, consequently it cannot be a globulin. The precipitate obtained from cultures of *a* was flocculent and perfectly white, but blackened on exposure to the air. The precipitate from cultures of A differed from the others, inasmuch as it was wholly insoluble in water. All of these precipitates were highly poisonous, and when injected under the skin of kittens and dogs caused vomiting and purging. Section showed the small intestines pale throughout and constricted in places. The heart was invariably found in diastole and filled with blood. The following brief notes illustrate the nature of the symptoms and the post-mortem appearances:

A small amount of the poison from X was dissolved in water and injected under the skin on the back of a kitten about eight weeks old. Within one-half hour the animal began to vomit and purge, and death resulted within eighteen hours. The mucous membrane of the small intestines was pale. The intestines were contracted in places and contained a frothy mucus. The stomach was distended with gas, and contained some mucus stained with bile. The liver was normal, the spleen and kidneys were congested, and the heart was distended.

A second kitten treated with the poison from bacillus *a* vomited and discharged from the bowels green matter. This animal died after fifteen hours, and presented appearances practically identical with those mentioned above.

A third kitten was treated with some of the precipitate from cultures of bacillus A, suspended in water, and presented substantially the same symptoms and post-mortem conditions.

Ten milligrams of the dried poison from bacillus *a*, injected under the skin of a guinea-pig caused death within twelve hours. Fifteen milligrams of the same substance was employed hypodermically on each of two kittens. One died after forty-eight hours, and the other recovered after two days of vomiting and purging. Two dogs, of about

five pounds weight, had each 40 mgm., and after serious illness of two days' duration speedily recovered. During these two days of vomiting and purging the dogs were constantly shivering as with cold, but the rectal temperature stood at from 102.5° to 103° F.

Under cheese poisoning I shall describe the chemical products of a bacillus found by Perkins and myself in cheese and ice-cream. Milk cultures of this germ are highly virulent, and the depressing action on the heart suggests that physiologically it belongs to the muscarine group.

Members of the colon group of bacteria frequently find their way into milk from udders foul with fæces from the cow. Some of these may induce an enteritis closely resembling typhoid fever. Such cases have been studied and described by Gaffky and Rehn.

Alt reports an epidemic of diarrhœa among children taking milk from cows fed upon bran made from grain contaminated with two kinds of mould. Alt supposes that either the bran contained poisons which were eliminated in the milk, or that the moulds elaborated chemical poisons in the intestinal tract of the cow, and these passed into the milk. He regards the former supposition as the more probable, since the cows showed no evidence of unusual irritation of the intestines. The milk was taken with attention to cleanliness and cared for in an unobjectionable way. It was always sterilized before being fed to the child. This emphasizes the great difficulty in protecting children against poisons that may be formed in milk.

Further researches on the galactotoxicons are much needed, but owing to the complex composition of milk cultures they are notoriously unsuitable for the isolation of chemical poisons.

The *treatment* of galactotoxismus should be prompt and energetic. The stomach should be thoroughly washed with a tube, the large intestines should be well irrigated with warm water, and then a pint of cool water containing from fifteen to thirty grains of tannic acid should immediately follow. Some of the galactotoxicons are either proteids or are held in close admixture with them, and are rendered less soluble by agents that precipitate proteids. After the stomach has been well washed, calomel may be given for its action on the small intestines. Irrigation should be repeated as soon as the vomiting or purging recurs. This may seem to be heroic treatment, especially in children, but these are cases of poisoning, and the poison may be removed more promptly and thoroughly and with less exhaustion to the patient if nature be aided by these means. Very small doses of atropine may be given hypodermically in those cases resembling muscarin poisoning. When the temperature goes to 103° F., an ice cap on the head is often beneficial. With a higher temperature the cold

bath with constant friction should be employed. The use of the coal-tar derivatives for the purpose of reducing the temperature is to be condemned. The administration of milk in any form is to be discontinued. This prohibition should be absolute and should hold until recovery. After the stomach has been washed, stimulants may be administered by the mouth. There is nothing better than whiskey, and this should be diluted with cold sterilized water.

The diapers of children suffering from milk infection should be disinfected, and, what is of more importance, the nurse's hands should be disinfected after she has removed the diaper.

Cheese Poisoning (Tyrotoxismus).

In order to avoid repetition I shall include under this heading the untoward effects that may follow the eating of not only cheese, but other milk products, as ice-cream, custard, cream puffs, etc. It is evident that any poison contained in milk may exist in the various milk products, and it is quite impossible to draw any sharp line of distinction beween galactotoxismus and tyrotoxismus. However, as I write this I find that I am attempting, unconsciously up to this point, to make a distinction and to avoid repetition. I have discussed under milk poisoning those galactotoxicons to which children are especially susceptible, and I will now proceed to a study of those bacterial poisons that may be formed in milk and its products and against which age does not give immunity. While this distinction cannot be sharply made, I fancy that for the purposes of this paper it will not be altogether devoid of merit. Milk is practically the sole food during the first year or eighteen months of life. Consequently, the effect of its poisons upon infants is of the greatest importance to the practitioner. On the other hand, milk products are seldom taken by the infant, while they are frequent articles of diet in after-life.

The tyrotoxicon discovered by the writer in 1884 has been so frequently mentioned and its action so fully described that it will be passed over in this article briefly. The symptoms induced by this poison usually appear within from two to four hours after the milk or milk product containing it has been taken. In a few instances the symptoms are delayed beyond this time and in these cases they are likely to be slight and transient. The severity varies with the quantity of the poison taken. At first there is dryness of the mouth followed by constriction of the fauces, then nausea, vomiting, and purging. The vomited matter at first consists of the food taken, then it becomes watery and may be stained with blood. The stools

also are at first semi-solid and then become watery and serous. The heart-beat grows weak and irregular, and in severe cases the face shows marked cyanosis. Dilatation of the pupil is seen in some, not in all. The vomiting and purging may be followed by great nervous prostration from which recovery follows slowly. In the most dangerous cases, those most likely to terminate fatally, the vomiting may be slight and soon cease altogether, and the bowels are constipated from the beginning. These are the cases demanding prompt and energetic treatment. The stomach and bowels should be thoroughly irrigated in order to remove the poison, and the action of the heart must be sustained.

Some writers seem to think that this tyrotoxicon is the only poison present in harmful cheese and other milk products. This idea is due to a misconception of the way in which these poisons are formed. I have demonstrated the presence of other poisons in these articles of food, and my studies lead me to believe that this is not the one most frequently present nor is it the most active one.

In 1890 I reported my further studies in poisonous cheese in the following words: "During the past two or three years we have received at the Hygienic Laboratory of Michigan University a number of samples of cheese which it was claimed had caused nausea and vomiting in those eating of them and in which we were unable to detect tyrotoxicon. Some of these samples produced vomiting and purging in cats and dogs to which the cheese was fed directly. The evidence that these samples had been the actual cause of the sickness of the people who had eaten them was thus confirmed by the experiments upon animals. But inasmuch as we were unable to detect the poison, we were compelled to report as follows:

"The poisonous character of the cheese has been proven by experiments upon animals, but we have failed to demonstrate the nature of the poison. Tyrotoxicon could not be detected.

"One sample of this class was found by Novy to be very poisonous. Some of this cheese was covered with absolute alcohol, and after standing in a dish for some weeks the alcohol was allowed to evaporate, then 100 gm. of the cheese was fed to a young dog and caused its death within a few hours. Sterilized milk to which a small bit of the cheese had been added after standing in the incubator at 35° C. for twenty-four hours became so poisonous that 100 c.c. of it introduced into the stomach of a full-grown cat caused death. Novy made plate cultures from the cheese, and from the spleen and liver of the dead animal, and succeeded in identifying one germ as common to both. Sterilized milk inoculated with a pure culture of this germ and kept in the incubator proved fatal to cats. But this

germ gradually lost its toxicogenic properties, which could not be restored by any of the methods tried.

"In a second class of samples the poisonous character of the cheese could not be demonstrated by direct feeding. Cats, rats, and dogs were fed with the same quantities as above mentioned without any appreciable effect."

The report made upon these samples was as follows: Animals fed upon the cheese were not affected. Tyrotoxicon could not be found. The sickness of the people was probably due to some other cause.

"The last sentence of this report was probably wrong, as will be shown by the following experiment: 2 kgm. of a cheese of this class were extracted repeatedly with absolute alcohol. The part insoluble in alcohol was then extracted with water. The aqueous extract after filtration was allowed to fall slowly into three times its volume of absolute alcohol. A voluminous flocculent precipitate resulted. After twenty-four hours the supernatant fluid was decanted and the precipitate was dissolved in water and reprecipitated with absolute alcohol; then it was collected and speedily dried on porous plates. A small bit of this precipitate was dissolved in water, and forty drops of this solution injected under the skin on the back of cats produced invariably within one hour vomiting and purging. After the partial collapse which followed the vomiting and purging, and which was evidenced by the animal sitting with its chin resting on the floor, recovery gradually followed.

"This substance belongs to the so-called poisonous albumins. From its aqueous solutions it is not precipitated by heat or nitric acid singly or combined. Its solutions respond to the biuret test. It is not precipitated by saturation with sodium sulphate, nor by a current of carbonic-acid gas; therefore it is not a globulin. It is precipitated by saturation with ammonium sulphate; and this fact removes it from the peptones."

In 1895 I was called upon to investigate a sudden death which was probably due to cheese. A man ate a lunch consisting of cheese, crackers, milk, and dried beef. Within an hour he complained of severe pains in his stomach. Ineffectual attempts were made by the physician who was summoned to induce vomiting and to move the bowels. Death resulted apparently from exhaustion twenty-two hours after the lunch. The cheese, it was said, had been in the house for three months and none of it had been eaten. I was furnished with only a small bit and the only chance of detecting a poison was by means of cultures. There was found in the cheese a bacillus, cultures of which after sterilization by filtration through porcelain

killed guinea-pigs, white rats, and rabbits. The nature of the poison was not ascertained.

In August, 1895, I received a glass jar containing a small quantity of ice-cream which had poisoned a number of people in a small village in northern Michigan. In October of the same year Dr. Morris, of Vassar, Mich., sent me a small piece of cheese which had caused alarming illness in a number of people of that place. These samples of suspected food were examined by Perkins and myself. The toxicogenic germs in the two articles were found to be the same, a fact which was suggested by the similarity in the symptoms observed and reported by the attending physicians at the two places. Some fifty people partook of the cream and all were more or less similarly affected. The number known to have suffered from eating the cheese was twelve. There were no deaths. The symptoms appeared from three to six hours after the food was eaten. The first evidence of illness consisted of nausea, which in all was followed by vomiting. Diarrhœa was present in the majority, but not in all. The vomiting was accompanied by sharp pains through the abdomen, and it is stated that in some the pain was relieved by pressure. The most alarming phenomenon observed by the physicians in attendance was feebleness of the heart's action. The head and feet grew cold, then the entire body became cool and clammy, and in many the radial pulse was not perceptible. This condition together with a heavy stupor in some gave occasion for alarm to the attending physicians, and hypodermic injections of brandy, digitalis, strychnine, and nitroglycerin were employed, each physician selecting the stimulant in which he had most confidence or taking that which happened to be at hand. In some the pupils were said to be dilated, but the evidence on this point is confined to the testimony of one physician. In one instance the patient became wildly delirious, crying out and attempting to rise from bed. Those who vomited but little and had no diarrhœa fell into a heavy stupor, and it is highly probable that these were in greater jeopardy than any of the others. The early and thorough vomiting doubtless was the most potent factor in saving those who had taken the larger part of the infected food. As has been stated, the depressing action of the poison on the heart impressed the physicians in attendance so markedly that all mentioned it, and one who had seen other cases of cheese poisoning thought that the active agent in this case must differ from that which had caused the illness previously observed by him.

The toxicogenic germ found in the ice-cream and cheese grows readily on the ordinary culture media. It begins to coagulate milk within from twelve to fourteen hours and later a heavy coagulum

forms and subsides and the fluid portion consists of whey. Milk cultures soon develop a pleasant odor of butyric ether, and this persists so long as the culture remains uncontaminated. The development of acid is accompanied by the liberation of gas. This continues until all the milk-sugar is consumed and for this a period of about one month in litre flasks is required. Milk rendered feebly red with rosolic acid is decolorized after two or three days in the incubator. This bacillus decomposes glucose, lactose, sucrose, maltose, dextrin, starch, and glycogen. It grows well on turnip, beet, sweet potato, onion, parsnip, carrot, banana, and apple. Attention is called to the fact of the ready growth of this bacillus on fruits and vegetables on account of the well-known observation that milk kept near decomposing fruits and vegetables frequently causes unpleasant symptoms in those drinking of it.

This germ is pathogenic to guinea-pigs, rabbits, cats, dogs, mice, and rats. Its virulence is increased by being carried through animals. In one series we employed fifty-one guinea-pigs, inoculating each with a culture made from the preceding animal. In all of this series the inoculations were made intraabdominally. Of the culture with which we began, 1 c.c. of a beef-tea growth twenty-four hours old was necessary in order to kill a guinea-pig of from 200 or 300 gm. weight within twenty-four hours; while of the cultures made from the animals near the end of the series, $\frac{1}{50}$ c.c. of like growth produced the same result. The decrease in the virulence of the germ when grown on the ordinary culture media is rapid, and the intensified virulence attained in the series referred to above disappeared in the third or fourth generation when grown in gelatin or agar. Milk seems to be the most suitable culture medium. We do not know that the germ multiplies more rapidly in milk than it does in beef tea, but cultures in the former are more virulent than those in the latter. The suspension of the germ in sterilized milk when the inoculation is made renders its action more certain. One-fiftieth of a cubic centimetre of a beef-tea growth of our intensified germ added to 1 c.c. of milk and immediately injected into the abdominal cavity of a half-grown guinea-pig invariably caused death within twenty-four hours; while an equal amount of the same culture added to beef tea and injected into companion animals caused death only after a much longer period, and in some cases failed wholly to do so.

The germ taken from the exudate in the abdominal cavity and used directly for the inoculation of another animal is more virulent than if it be carried through a culture medium before the inoculation is made. The number of germs in 1 c.c. of such a peritoneal exudate was determined in one instance and found to be 34,800,000. One

one-hundredth of a cubic centimetre of this fluid injected into the abdominal cavity of a guinea-pig weighing 350 gm. caused death within twenty hours, while one-half of this quantity failed to cause any visible effects. It will therefore be seen that the number of germs in the most virulent culture necessary to kill a half-grown guinea-pig when injected intraabdominally is somewhere between 348,000 and half that number. When given subcutaneously larger amounts are necessary to cause death.

Two litre flasks, each containing one litre of sterilized milk, were inoculated with the germ taken directly from the peritoneal cavity of a guinea-pig. These flasks were kept in the incubator for thirty days. The contents were then filtered through paper. As soon as the pores of the paper were coated with the proteid part of the culture, the filtrate became not only perfectly clear, but sterile. Thus the slow filtration through porcelain practised in our first experiments became unnecessary. From 5 to 10 c.c. of this filtrate injected into the abdominal cavity of full-grown white rats or half-grown guinea-pigs caused death within less than one hour. These filtered cultures were then distilled in vacuo at a temperature not above 40° C. until there remained in the retort not more than 100 c.c. The distillate was acid and had the pleasant odor of the original culture; 10 c.c. failed to induce any symptoms in rats. Five cubic centimetres of the concentrated fluid in the retort killed rats within five to ten minutes. This concentrated fluid, which was strongly acid, was shaken twice with double its volume of ether. On spontaneous evaporation the ether left a very small residue, which sometimes contained a few imperfect crystals. This residue injected into a full-grown rat killed it within four minutes. The above experiment was repeated many times, and although the quantity of poison left on the evaporation was found to be variable, it was never altogether wanting. In some instances the residue from the ether consisted of a few drops of a brownish, oily semi-fluid. In others the residue was perfectly dry, and when examined under the microscope showed some granular matter mixed with a few imperfect prisms. The removal of the poison from the concentrated fluid is imperfect and incomplete, as was shown by driving off the traces of ether from the fluid by keeping it for days in vacuo at 40°, and then injecting some of it into animals, when death resulted quite as promptly as before the extraction with ether was made. When this method was employed with Uschinsky cultures, the amount of the poison left on the evaporation of the ether was much less than that obtained from an equal volume of milk culture. The animal dies, but not until several hours after the injection. We have not been

able to obtain enough of the poison to enable us to identify it chemically.

Many other methods of isolation have been attempted but without success. The distillation was in several instances continued in vacuo until only a syrupy residue remained. The residue was extracted with absolute alcohol, which dissolves the poison, the alcoholic extract was evaporated, and this residue was again treated with absolute alcohol. This was repeated as many as a dozen times and the alcoholic solution was finally precipitated with platinum chloride. This precipitate was crystallized, but was found to consist of a sodium salt.

In another experiment the residue obtained after repeated extractions with alcohol was distilled in vacuo at a high temperature. At 130° C. a clear fluid passed over, but this consisted of glycerin containing only traces of the poison as was demonstrated by its action on animals, while the residue in the retort was found to be inert.

From the concentrated filtered culture when made alkaline with either ammonia or a fixed alkali, the poison is not removed by ether. This distinguishes the poison chemically from tyrotoxicon. Physiologically this poison is distinguished from tyrotoxicon by the more pronounced effect of the former on the heart, in which it resembles muscarin or neurin more closely than it does tyrotoxicon. Pathologically the two are unlike inasmuch as the product of this bacillus induces marked congestion of the tissues about the point of injection or in the peritoneum when thrown into the abdominal cavity. Moreover, the intestinal constriction which was so universally observed in animals poisoned with tyrotoxicon has not been once seen in our work with this new germ and its poison, although it had been carefully looked for in the more than two hundred animals experimented with.

The poison is not removed from either acid or alkaline solutions with chloroform.

The following experiment was made in order to determine whether or not our bacillus elaborates a proteid poison or a toxin which is precipitated with the proteids. For this purpose an Uschinsky culture was selected, inasmuch as such a culture contains no proteids save those elaborated by the germ. A litre of an Uschinsky culture forty days old was filtered through porcelain in order to remove the germs. The clear, strongly acid filtrate was allowed to fall, drop by drop, into twice its volume of absolute alcohol. A flocculent white precipitate fell and formed a thin layer on the bottom of the cylinder. This precipitate was collected on a filter and washed for two days with absolute alcohol. It was then

dried between folds of filter paper and rubbed to a powder in an agate mortar. Twenty milligrams of this powder suspended in water was injected into the abdominal cavity of a guinea-pig. The animal showed no effect of the poison at the time, but it died two days later. Post-mortem examination showed the same condition as had been observed after death from inoculation with the bacillus and after death from the poison extracted with ether. The peritoneum was highly congested, the abdominal cavity contained a reddish exudate, and the heart was in diastole and filled with blood. It may be that enough of the same poison which is extracted with ether had been carried down mechanically with a non-poisonous proteid, and had not been removed by the repeated washings with alcohol. If this is the case or if there are two chemically distinct poisons, we are not able to determine at present. The Uschinsky fluid which had been treated with two volumes of absolute alcohol and from which the alcoholic precipitate had been removed as just stated, was concentrated in vacuo and the concentrated fluid was shaken with two volumes of ether, and the residue left on the evaporation of the ether injected into a guinea-pig caused death within four hours. Post-mortem examination showed the condition already described as due to the germ and the germ-free cultures.

As has been stated, the action of the poisonous agent in this cheese resembles that of muscarin and neurin. The theoretical explanation of the presence of neurin among bacterial products has been given elsewhere. I believe that when the poison of this bacillus is isolated it will be found to be closely akin to neurin chemically as well as physiologically.

The "knetkäse" of Norway is frequently poisonous. According to Holst it is prepared in the following manner: Skimmed sour milk is placed in a kettle and heated until the casein coagulates. The coagulum is put into a linen bag and allowed to drain, when it is transferred to a wooden vessel and mixed with salt by vigorous kneading with the hands. It is this process of kneading that gives to it the name "knetkäse." Some of the more cleanly mix the salt and cheese with a large spoon, but usually the hands are employed in kneading the mixture. The vessel containing the cheese is now set away for the ripening process. This requires from a few weeks to as many months, during which time the cheese often remains on the shelf over the cook stove. After the ripening process reaches the desired stage, which depends largely upon the taste or fancy of the maker, the cheese is mixed with caraway seed. In doing this the hands are again usually employed. The food is now ready for the table. In poisonous samples of this cheese Holst found virulent

forms of the bacillus coli communis. Cultures of this germ obtained from the cheese and given to calves in milk cultures caused diarrhœa and in some cases death.

In the great majority of instances of cheese poisoning, nature's efforts to eliminate the poison are sufficient. As in other forms of bromatotoxismus the greatest danger exists when vomiting is slight and transient and purging is absent. In the muscarin-like cases the action of the heart must be closely watched, and it is probable that atropine is the best physiological antidote.

Vanilla is frequently employed in flavoring custards, ice-cream, and other milk products, and the poisonous effects following the eating of these foods have often been attributed to this flavoring. I have investigated several instances of this kind, and in one of these Novy and I positively demonstrated the harmlessness of the flavoring by swallowing the three drachms of the vanilla extract left in the bottle from which the custard had been flavored. I do not believe that either the natural or the artificial vanilla is sufficiently toxic to harm one in the quantities in which it is used in flavoring custards, etc. It is stated, however, by the Mexican dealers that a poisonous bean is sometimes mistaken for vanilla. I am not prepared to confirm or deny this statement. Morrow makes the following statements: "In preparing vanilla for the market, the vanilla pods are classified according to their size and quality, the quality depending upon the more or less abundance of a substance which exudes from the pod and crystallizes upon the surface in the shape of white frost-like needles. In order to prevent the dissemination of these crystals, the pods are frequently covered with a protective coating of the oil of the cashew nut. Cardol, or the oil of the cashew, is a most powerful irritant, simple contact with the skin causing vesicular, erysipelatous, and other cutaneous eruptions. Artificial 'vanillin,' as it is termed, is made from coniferin, found in the sap of the pine. In the manufacture of this extract, bichromate of potash, an exceedingly irritating substance, is largely employed. It is hardly probable that the process of purification is so perfect as to remove all traces of this agent."

That there may be enough bichromate of potassium in vanilla extract to render each teaspoonful of the custard or ice-cream sufficiently poisonous to induce persistent vomiting, purging, and marked prostration seems to me to be highly improbable to say the least. Moreover, as has been stated, the fact that the flavoring did not in the case studied by me constitute or contain the poison was demonstrated by taking as much of the vanilla as was used in flavoring gallons of the custard without effect, while a teaspoonful of the cus-

tard caused nausea and vomiting. Milk products flavored with other extracts and those wholly without flavoring have frequently proved to be poisonous. Vanilla extract has acquired the reputation of being poisonous because it is so frequently used in milk products and these often become harmful from bacterial infection. There is no positive evidence in medical literature known to the writer that any such form of poisoning as vanillismus ever occurs.

Vegetable Food Poisoning (Sitotoxismus).

Under the heading of sitotoxismus I shall include all forms of poisoning with vegetable foods infected with moulds and bacteria. All sitotoxicons are not bacterial products. However, for completeness it will be necessary to go a little beyond the proper scope of this paper. It is needless to state that I shall not include under this heading cases of poisoning due to admixture with mineral poisons. I shall also attempt to exclude as far as possible a discussion of plants that are in and of themselves poisonous.

Ergotismus.

Ergotismus, or, as it is sometimes called, ergotism, is due to poisoning with a fungus known as claviceps purpurea, which develops in the flowers of rye, other grains, and certain wild grasses. Ergot is most frequently found in rye and darnel. Early in the development of the rye flower there may appear in its interior a sweet, unpleasant-smelling liquid. This liquid sometimes forms so abundantly that it overflows, runs down the stalk, and falls upon the ground. The sugar which it contains attracts ants and other insects, and these aid in the distribution of the fungus. This sweet liquid is ordinarily known as the honey-dew of rye. In the rye flower there now develops a fungus which is known as ergot. There are certain conditions which are known to favor the development of this parasite. It is more common when there is a rainy spring followed by a hot dry summer. Thorough cultivation of the soil kills out this parasite, and for this reason ergot is more abundant in countries where the soil is not well cultivated. Within recent years epidemics of ergotism have been observed only in Russia and in Spain. As an epidemic disease ergotism is unknown in the United States. Bird, however, reports an epidemic of ergotism in cattle in Kansas in 1895. The disease was due to ergot in wild rye fed to the cattle. (See Twelfth and Thirteenth Annual Reports of the Bureau of Animal Industry.) Sporadic cases of ergotism due to the medicinal use of this drug, or to its too long-continued employment, are occasionally seen. Ergot

has been much employed by ignorant and criminal medical pretenders as an abortifacient. The continued use of ergot is necessary in order to develop its most disastrous effects. However, acute ergotism, as will be seen later, may be due to a few large doses. Grains of ergot, after having been exposed to the air for a few months, lose in large part their toxicity. For this reason epidemics of ergotism follow closely upon the harvests, and especially upon poor harvests, when the parasite is most abundant, and the people are compelled to feed upon what they have without close inquiry as to its quality. However, it may be pointed out here that in the present state of civilization there is but little excuse for the existence of epidemics of ergotism. In the first place thorough cultivation of the soil would soon completely eradicate this mould. A proper selection of seed would also do much in the same direction. Kühn as early as 1858 pointed out the benefit that would be secured by an early harvest of fields contaminated with ergot, as by this means the spread and subsequent development of this parasite would be prevented. Moreover, the ergot grain is much larger than that of rye, and this difference of size permits of the easy separation of the two by means of sieves specially constructed for this purpose. The commercial value of ergot is so much greater than that of rye that the time given to the separation of the two would be profitably spent, and yet so dense is the ignorance and so pronounced is the indolence of certain peasant classes in Russia and Spain that epidemics of ergotism continue and probably will continue for many years.

It will be impossible to give any extended account of the chemical researches which have been carried on with a view of determining the active principle or principles of ergot. Scarcely any other drug has been studied by so many chemists with such diverse and contradictory results. The separation of the active principle has been frequently announced, but a preparation that has been heralded by one investigator as the possessor of all the virtues of the crude drug has been pronounced by another as devoid of all action. Kobert and his student Grünfeld have found three poisons in ergot. These substances are ergotinic acid, sphacelinic acid, and cornutin. The first of these, ergotinic acid, is poisonous when injected subcutaneously or intravenously, but seems to be devoid of poisonous properties when taken by the mouth. Therefore it can play no part in the causation of ergotism. Jacobi states that he has obtained from ergot a chemically pure substance having the formula $C_{21}H_{22}O_9$, and he believes this to be the active principle of the so-called sphacelinic acid. In all cases of ergotism both the sphacelinic acid and the cornutin are contained in the ergot. Therefore a clinical picture of the disease

must be a composite resulting from the combined action of the two, and it must vary with the preponderance of one or the other in the ergot taken.

It is believed that sphacelinic acid is the constituent of ergot that causes gangrene and develops the cachexia of the disease. Pure sphacelinic acid without any admixture with cornutin would cause ergotismus gangræenosus. Grünfeld fed animals with sphacelinic acid and induced gangrene in all. In cocks, gangrene soon appeared in the comb, then in the wattles, tongue, wings, and crop. The ears of hogs to which this acid was fed fell off bit by bit. Horses and cows lost their tails, ears, and hoofs. In dogs and cats the gangrene usually began in the skin. When locally applied in concentrated solution sphacelinic acid causes gangrene of the tissues with which it comes in contact. This easily explains the necrosis of the epithelial tissues, the ulcerations, and the hemorrhages in the intestines. If sphacelinic acid be applied in more dilute solution, local gangrene does not occur, but changes which differ from gangrene only in degree are observed. In this way we may account for the degeneration of the walls of the blood-vessels and the extravasations which follow upon these changes.

Cornutin does not cause death of tissue, but acts directly upon the nervous system, and is believed to be the active agent in the causation of ergotismus convulsivus. It acts on the brain and cord affecting the vagus and vasomotor centres, and acting through the lumbar cord on the uterus. Cornutin readily undergoes decomposition and gradually loses its virulence. It is found only in fresh ergot, disappearing more quickly than the sphacelinic acid. For this reason it happens that those symptoms due to cornutin are more prominent in outbreaks occurring soon after the harvests; while those due to sphacelinic acid are seen in both early and late epidemics.

There are some reasons for believing that there are bacterial products formed in ergotized bread. To these has been attributed the septic character of certain epidemics of ergotism. However, this is mere supposition, and there has been no scientific experimentation made in its support. It is easy to see how sepsis occurs in ergotism without the necessity of supposing the presence of bacterial products in ergotized bread. In gangrene of the intestines bacterial infection through the diseased intestinal walls may easily occur. In gangrene of the skin infection from without may take place with equal readiness.

As has been stated, acute ergotism is the form most frequently, in fact quite exclusively, observed in this country. In its mildest

forms it is characterized by gastrointestinal and vasomotor symptoms, loss of appetite, nausea, salivation, vomiting, diarrhœa, colic pains, formication, muscular weakness, and feebleness of the heart's action, are the most prominent symptoms. When very large quantities of ergot are taken, dizziness, headache, mydriasis, loss of consciousness, or delirium, coma, and failure of the heart's action have been observed. If the sufferer be pregnant, abortion usually occurs. Following abortion there is often free and dangerous hemorrhage. Acute ergotism terminates in death or recovery within a few days. It is generally due to the excessive administration of some medicinal preparation.

Chronic ergotism is best studied under the two forms, ergotismus convulsivus sive spasmodicus and ergotismus gangrænosus.

Symptoms similar to those of the milder form of acute ergotism usually constitute the first manifestations of the convulsive form. After these have continued for some weeks more markedly nervous symptoms appear. Specks float before the eyes, ringing noises are heard constantly in the ears, there is dizziness, and the gait becomes unsteady. Irritation of the skin and formication make life a burden. The special senses become benumbed, the sight loses in keenness, there is a tendency to somnolence, mental perceptions become less acute, an epileptic condition sets in, and hebetude results. Convulsive seizures occur and sometimes continue for hours. In these spasms the flexors overcome the extensors. The hand is bent upon the wrist, and the fingers are partially closed. These contractions become after a while more or less permanent. Different groups of muscles become involved in different subjects. Hydrophobia may be closely simulated on account of spasm of the œsophagus and of the diaphragm. Opisthotonos, emprosthotonos, and trismus have been observed. A few weeks after the appearance of the initial symptoms, the tendon reflex is lost and the symptoms resemble those of tabes dorsalis. Pain in the legs may be constant, and a girdle sensation is frequently complained of, and Romberg's symptom, which consists of increased incoördination of movement on putting the feet together and closing the eyes, becomes prominent. The more characteristic symptoms of locomotor ataxia may be developed. Psychical disturbances are often very marked. Melancholia is frequent, and a condition resembling that of paralytic dementia is very often found in great epidemics of ergotism. In the first stages of this form of ergotism the pulse becomes small, the extremities grow cold and the skin pale, the temperature falls below the normal, and chilly sensations and cold sweats are frequent. The hair falls out, the nails cease to grow, and the epidermis upon various parts of the body may

be raised in blisters. Nutrition is necessarily interfered with, and a marasmic condition supervenes.

The initial symptoms of ergotismus gangrænosus consist of pain in the back, formication, muscular contractures, chilly sensations, heaviness in the limbs, and general weariness. The toes or fingers, or both, take on an erysipelatous redness, and gangrene sets in. This gangrene is usually dry, and there is neither hemorrhage nor suppuration unless bacterial infection results. The phalanges of the toes or fingers, the feet or the hands, the legs or the arms, may necrose and fall off. The external genital organs are sometimes involved in these necrotic changes, and gangrenous patches may appear on the skin over any part of the body or in the intestinal mucous membrane.

When it exists in epidemic form there is but little difficulty in the *diagnosis* of ergotism, but in sporadic cases there may be great perplexity. The recognition of the acute form must depend largely upon the history, and upon the exclusion of other diseases. If the uterus be affected a valuable aid to diagnosis is thereby afforded. Acute ergotism may be mistaken for poisoning with phosphorus, arsenic, or antimony. Certain septicæmias may also resemble ergotism. When due to the eating of ergotized bread, an examination of the vomited matters for ergot may be of great service. However, when the drug has been administered in the form of some medicinal preparation this aid to diagnosis is unnecessary.

The convulsive form of ergotism must be distinguished from epilepsy, hydrophobia, tabes, and tetany. Usually the history of the case will be sufficient to enable the physician to differentiate ergotism from the above-mentioned diseases. The subnormal temperature which generally prevails in ergotism will ordinarily distinguish it from any of the infectious diseases.

The gangrenous form is generally easily recognized. However, when ulceration of the intestine occurs and is followed by hemorrhage, the trouble may be mistaken for typhoid fever, but generally in ergotism gangrene begins in the extremities.

Prognosis in this disease will depend very largely upon the stage reached. In acute ergotism the prognosis must be determined by the extent to which the heart is affected. We must also take into consideration the form in which the poison has been administered and the amount taken. In the convulsive form recovery may occur even after the seizures have become pronounced. In the gangrenous form the extent of involvement is easily recognized and will form the chief basis for a prediction of the ultimate result.

Post-mortem examinations in fatal cases show no constant or

characteristic lesions in the thoracic or abdominal viscera. The extensor muscles of the limbs are usually atrophic. Microscopical examination shows a toxic polyneuritis which is classed by Leyden among those forms of neuritis produced by lead, mercury, arsenic, antimony, phosphorus, carbon disulphide, carbon monoxide, and alcohol. In five cases carefully examined Tuczek found hyperplasia and fibrillar metamorphosis of the neuroglia at the expense of the nerve elements in the posterior columns of the gray matter.

The proper *treatment* of acute ergotism consists of washing out the stomach and large intestines, and the administration of calomel or castor oil for the purpose of cleansing the small intestines. Such astringents as tannic acid and bismuth subnitrate may be indicated. Finally, opium may be necessary in order to allay the intestinal irritation. It has been found that in threatened abortion from ergot cold-water vaginal douches are of great value. However, if abortion has already occurred, the uterus should be thoroughly cleansed with all the attention to detail given to abortion from other causes. In threatened failure of the heart, alcohol, coffee, camphor, acetic ether, one or more, according to the indications, may be beneficial.

In the chronic forms of the disease the first thing to be done is to see that the patient is no longer supplied with ergotized bread. Indeed, it is the experience of those who have had to deal largely with this disease, that restriction to animal food for some days is of benefit. Even in the chronic form the stomach and bowels may be washed out with advantage. To start with, calomel is the best intestinal antiseptic, but later salol may be found to be more suitable. The chronic diarrhœa so frequently observed in this disease is best treated by intestinal irrigation and the use of astringents. Opiates may be necessary. Nitrite of amyl and nitroglycerin have been found to be of value in the convulsive form. Chloroform narcosis has been tried but without result in prolonged spasms. The epileptic seizures are more amenable to chloral hydrate than to bromides. Massage and electricity have proved of some value in treating the paralysis of the extremities.

In the treatment of the gangrene of ergotism special attention must be given to the prevention of sepsis. Local lukewarm antiseptic baths and mild mustard sinapisms are of value. Strychnine is probably the best heart tonic in these cases. Proper nourishment and suitable sanitary surroundings are of great value. Amputation of the gangrenous part is often necessary, but this should be delayed until the line of demarcation is well defined.

Lathyrismus.

Lathyrismus or lathyrism is a form of spastic spinal paralysis due to intoxication from the eating of the seeds of certain species of the genus lathyrus of the vetch tribe. There are more than one hundred and twenty known species of lathyrus. Of these, thirteen are native to the United States, and others are cultivated here on account of their showy flowers. The common sweetpea of the garden is an example of the latter. In Northern Africa and Southern Europe lathyrism has been frequently observed. It is also known to occur in India and other parts of Asia. The species that have been best studied are lathyrus sativa, German vetch, lathyrus cicerea, red vetch, and lathyrus clymenum, Spanish vetch. In Italy and Algiers the grain fields are sometimes so filled with vetch that the use of bread made from the mixture of the grain and the seeds of this plant causes poisonous effects. In some places vetch is cultivated as a food for the lower animals, and in times of great scarcity the seed mixed with wheat, rye, or other grain is used as a food by man.

The literature of lathyrism has been collected by Schuchardt,[1] and I will refer those who desire a more complete history of the disease to his article. It seems that formerly lathyrism was much more extensive than it is at present. As early as 1671 it was known that bread made of vetch seeds mixed with grain seriously affected those who ate of it for any length of time. In the above-mentioned year the Grand Duke of Würtemberg issued an edict forbidding the use of food of this kind. A similar command was repeated by his successor in 1705, and again in 1714. It was then noticed that those who ate of this bread suffered from a marked stiffness of the extremities. The disease was regarded as incurable, although death seldom or never resulted from it. In 1691 an epidemic of lathyrism was reported in the Grand Duchy of Modena. In 1784 Tozzetti reported an epidemic in Tuscany due to the fact that the people on account of the scarcity of food were compelled to nourish themselves on chick peas. It was observed that the disease in this epidemic began with great weakness in the lower extremities, and some lost the power of locomotion either in part or altogether. All those in whom this paralysis was observed had eaten for three months or longer a bread made of two parts of chick pea and one part of rye or wheat. The peas used in this epidemic had been imported from Tunis. Tozzetti planted some of these seeds and after their growth identified them as lathyrus sativa.

Desparanches studied an epidemic of lathyrism in France in 1829. The sickness in this case was due to the eating of bread made from

equal parts of chick peas and grain. Desparanches believed that the seat of lesion characteristic of the disease was in the lumbar cord. He observed convulsive movements of the muscles of both the thighs and legs. This symptom was followed by complete inability to walk. About the same time an epidemic was reported in India, where on account of two successive harvest failures the people were compelled to resort to vetch as a food. Some of the cases of paralysis occurring in the Indian epidemic were under the observation of English physicians for several years, and it was stated that recovery was unknown. Since the above-mentioned date many local epidemics have been reported by English physicians in India. In one of these reports Irving has shown that the claim that lathyrism and beriberi are identical cannot be sustained. He states that beriberi is a disease from which the afflicted may recover, either from the employment of medicinal agents or from change of climate, while from lathyrism there is no recovery after the development of paralytic symptoms. Furthermore, he states that in beriberi the arms and the muscles of the chest are involved, while in lathyrism the symptoms are confined to the lower extremities. In the latter there is neither contraction of the fingers nor a sensation of numbness in the affected muscles. Lathyrism does not cause death, while beriberi does, and in the former the patient may remain in fair health for many years with the exception of his inability to walk.

Numerous attempts have been made to isolate the poisonous principles of lathyrus. The results that have been obtained so far are unsatisfactory and to some extent contradictory. Teilleux obtained a resinous body which when administered to rabbits in gram doses caused tetanic movements of the muscles, and finally paralysis of the posterior extremities. Death occurred in these animals in about four days. From lathyrus cicerea, Bourlier obtained an extract which killed frogs and small birds within forty-eight hours at most. An injection of two drops of this extract diluted with five drops of water into a sparling was followed by the following symptoms: Almost immediately a marked diarrhœa appeared; this was accompanied by persistent vomiting. The feathers became ruffled and the bird sat in a crouching position. The heart beat rapidly and the respirations were hastened and difficult. The muscles of the legs soon became paralyzed, those on the left side being more markedly affected. Birds treated in this manner lived from ten to twenty-four hours. This extract induced in turtles at first a period of excitement marked by unusual muscular movements and accompanied by profuse diarrhœa. Subsequently there seemed to be complete inability of movement, and this was followed by death. An

alkaloidal body was obtained by Marie from the seeds of lathyrus sativa. However, this substance when administered subcutaneously to guinea-pigs failed to induce any of the characteristic symptoms of lathyrism. Astier extracted the seeds with dilute alcohol, keeping the temperature during the process of extraction below 50° C. Two decigrams of this extract was injected subcutaneously into a dog weighing 8.5 kgm. Ten minutes later there was noticed a trembling of the posterior extremities which ceased after one-half hour. Twenty-four hours later a second injection containing 6 dgm. was administered to the same animal. The trembling was now more pronounced and was followed by partial paraplegia. Twenty-four hours later, a third injection consisting of 8 dgm. was administered. This was followed by convulsive movements, and after half an hour by complete paraplegia. From this condition the animal slowly but completely recovered. This experiment was repeated on three other dogs with like results. Astier satisfied himself that the seeds from which this extract was made were free from any contamination, and that they did not contain any mould. The same investigator obtained from the seeds of lathyrus cicerea a volatile alkaloidal body to which he gave the name lathyrin. He states that this substance is of a doughy consistence, strongly alkaline, insoluble in water, slightly soluble in ether, but freely soluble in chloroform, and easily volatile. It was found to be readily soluble in dilute hydrochloric acid. Its hydrochloric-acid solution responded to the general alkaloidal reactions. On the evaporation of this solution the residue was found to consist of needles, and these on being heated on platinum foil burned without residue. Unfortunately there is no record of physiological experimentation with this substance, and consequently there is no evidence that it constitutes the active agent of the seed. Some observers stoutly maintain that the seeds of lathyrus are harmful only when decomposed, or when they contain some parasitic growth similar to ergot. Others believe that the poisonous symptoms are due to the mixture of these seeds with those of other plants such as agrostemma githago (corn-cockle), and lolium temulentum (darnel).

There are good reasons for believing that whatever the poisonous substance may be, it is destroyed at a high temperature. The Arabs of Northern Africa eat vetch prepared in two ways. One of these dishes is known as "kouskouson," and in its preparation the seeds are steamed or boiled; while the other dish, known as "galette," is cooked at a higher temperature, and it is said to be a well-authenticated fact that injurious effects more frequently follow the use of the former than of the latter.

The fact that vetch seeds are poisons to many of the lower animals has been abundantly demonstrated by direct experimentation. Gabory fed eighteen ducks with vetch seeds ground with corn. All the birds died on the first day, with symptoms of intoxication—somnolence and paralysis. Similar experiments with like results were made on geese and pigs. Pigeons were found to be less susceptible, and indeed were supposed by this investigator to be wholly immune to the poison. The statement has been made that animals are never affected by eating the green plant. This is denied by some, and Ferrarisi states that he saw eighteen hogs paralyzed in their posterior extremities after feeding upon green vetch. In 1867, on account of the high price of oats in France, the proprietor of a line of omnibuses sought for some cheaper food for his horses. Vetch seed was recommended on account of its high nutritive value as determined by chemical analysis. An experiment was made on forty-five horses, while the others belonging to the same line and numbering one hundred and fifty were kept on their accustomed food. At first two litres of the vetch seed were mixed with thirteen litres of oats. This mixture not being relished by the horses, the proportion of the seed was reduced to one to thirteen. The feeding of this mixture was continued for some months. The first symptoms of poisoning made their appearance about the expiration of the second month. The most marked symptoms were dyspnœa and asphyxia. Tracheotomy was performed on some of the animals. Verrier states that there was paralysis of the recurrent laryngeal nerve. The muscles of the larynx were found to be greatly atrophied. Microscopical examination showed these muscles to be without striation, and to be undergoing fatty degeneration. More chronic poisoning caused paralysis of the posterior extremities and death.

Cantani believes that the characteristic lesion of lathyrism is to be found in the muscular fibres, and that the intramuscular nerve branches are not affected. He cut a small bit of muscle from the leg of a well-developed case and found on microscopical examination that the transverse striations were indistinct and that the muscle was infiltrated with minute fat drops. However, the weight of evidence renders it fairly certain that the nerves as well as the muscle are affected.

In man the first *symptom* of lathyrism usually manifested is a chill, which is followed by pain in the loins and legs. A girdle sensation is complained of by some. Motor lameness of the lower extremities is common. The patient walks with difficulty, and later he finds locomotion wholly impossible. The knee reflex is greatly intensified. Paræsthesia with formication may be marked. It is

claimed by some that gangrene in the feet and legs may occur. However, it is possible that these may have been cases of ergotism. Incontinence of urine and impotence are common and early symptoms. The old belief that recovery never occurs is not supported by more recent observations. Many of the milder cases are greatly improved by proper medicinal treatment.

The prophylactic treatment of lathyrism is the most important. When the disease is developed it is to be treated as spastic spinal paralysis of myelitis due to other causes. The application of irritants such as a mixture of tincture of iodine and croton oil, and the use of the actual cautery to the lumbar spine have been found to be of value. Warm baths, galvanization, and faradization have been recommended. Bromide of potassium in gram (fifteen-grain) doses repeated from three to six times per day has been found to be of most value. Strychnine and quinine are not only without value, but are apparently harmful.

Maïdismus.

Maïdismus, ordinarily known as pellagra, may be defined as a progressive disease leading to paralytic and other nervous disorders, and caused by intoxication from the eating of damaged Indian corn. The first historical account of this disease comes from Spain, where it appeared in the neighborhood of Oviedo in the year 1735. Its geographical distribution is confined to that portion of Europe lying between the parallels of 42° and 48° N., with the exception of Corfu, one of the Ionian islands. Within the above-mentioned region pellagra is by no means universally or evenly distributed. However, it prevails in some localities to such an extent that it has become a national calamity. In 1879 one hundred thousand cases of this disease were reported in Italy, and in 1881 fifty-six thousand in Lombardy lone. Pellagra is confined to countries where the staple article of diet is maize, and yet Indian corn constitutes a most nutritious and healthful article of food in other countries. This statement has been abundantly demonstrated by the former well-nourished condition of the large colored population of the Southern United States, for there probably never has been a class of day laborers, certainly never a class of servants, better fed and nourished than were the negroes of the South before their emancipation; and corn bread made from mature corn and properly prepared is both healthful and nutritious. Pellagra is known only in those countries where on account of an uncongenial climate, or from barrenness of the soil, or from lack of proper cultivation, maize does not mature. One author states: "Although Lombardy is the garden of Italy, its peasants are over-

worked, underpaid, and underfed; instead of a diet suited to their severe labor, their sustenance consists largely of the more worthless kinds of Indian corn of their own growing, the produce of poorly cultivated ground, sown late, harvested before maturity, and stored carelessly in its wet state; even if they grow a certain proportion of good maize, the millers, to whom they are often in debt, are more likely to grind the worst samples for the peasant's own use. The flour is either made into a kind of porridge—the 'polenti' of Italy, the 'cruchede' of Gascony, or the 'mamaliga' of Roumania—or it is made into loaves, without yeast, baked hastily on the surface only or on one side, and raw and wet within, large enough to last a week, and apt to turn sour and mouldy before the week is out."

There can no longer be any doubt that pellagra is an intoxication due to poison formed in cornmeal or bread. However, we have no positive information concerning either the ferment which causes these harmful changes or the poisonous substance or substances that are formed. Some think that the disease is an intestinal mycosis, due to infection with a parasitic mould which is introduced into the body with the food. Carboni has found in the damaged meal used by pellagrous persons, also in their fæces, a bacterium to which he has given the name bacillus maïdis, and to which he ascribes the disease. Majocchi claims to have found this germ in the blood of pellagrous individuals. According to Paltauf and Heider the grains of corn become infected during the wet season with the bacillus maïdis and the bacillus mesentericus fuscus, and these bacilli decompose the moist meal producing maize ptomaïns which are the active poisonous agents. Others claim that the so-called bacillus maïdis is nothing more than the widely distributed potato bacillus, that it is incapable of generating poisonous products under any conditions, and that it is by no means constantly found in the intestines of pellagrous individuals.

Lombroso claims that the disease is an intoxication rather than an infection. He believes that certain chemical poisons are formed by bacterial activity, and that these poisons induce the disease. This investigator has obtained from powdered corn which has been allowed to ferment at from 25° to 30° C. for twenty-four to thirty-six hours an alcoholic extract and an oily substance, and with these he states that he has induced the characteristic symptoms of pellagra in man and in animals. The alcoholic extract of this corn contains a basic substance or substances to which Lombroso has applied the name pellagrocin. His theory is that there are two different poisons, and that their combined action gives rise to the complex symptoms of pellagra, similar to the action of sphacelinic acid and cornutin in

ergotism. One of these poisons he thinks has a strychnine-like effect, while the other is narcotic in its action.

Neusser believes that there is nothing directly harmful in the food when it is taken into the body, but that poisons are formed from the constituents of the foods in the intestines. He makes the disease a specific form of autointoxication. It is claimed that sporadic cases of pellagra may be due to the use of whiskey made from damaged corn. If this be true the poisonous substance must be volatile. New cases of pellagra occur most frequently during the spring, and especially during wet seasons.

This disease is believed to consist of three stages more or less marked and distinct. The first stage begins with disturbances of the digestive organs, the tongue is at first heavily coated but later it loses its epithelium, there is loss of appetite as a rule, although in exceptional cases the desire for food may be inordinate. The stomach seems swollen and often painful. Usually there is diarrhœa, but obstinate constipation may occur. Accompanying these digestive disturbances, there is pain in the head, neck, and back. Dizziness, muscular weakness, and unsteadiness of gait are frequently observed. Mental activity becomes slow and some complain of a numbness in the brain. In the majority of instances, not in all, there is a characteristic erythema which is most marked on the unclothed parts of the body, as the hands and face, though it may be much more widely distributed. It is to this affection of the skin that the disease owes its common name pellagra (from *pelle*, skin, and *agra*, rough).

The appearance of certain cerebrospinal symptoms characterizes the second stage of the disease. Chilly sensations are complained of. There is constant ringing in the ears. The muscular weakness is increased; tremors and convulsive twitchings become frequent, cramps and light spasms occur. The tendon reflex is more markedly exaggerated, sensibility is often diminished, and the patient falls into a state of melancholia. The skin becomes very pale or there is capillary injection over certain areas, notably of the face. The erythema becomes intensified each spring, and the skin becomes dry, shrivelled, inelastic, and dark brown. In some instances, especially in chronic cases, the skin becomes hard and scaly.

Marked emaciation is one of the characteristic symptoms of the third stage. The subcutaneous fat wholly disappears, locomotion becomes impossible, incontinence of urine is persistent, and uncontrollable diarrhœa makes the bed-ridden patient an object of pity. Fortunately, after this stage has been reached the individual loses all resistance to the infectious diseases and tuberculosis or septicæmia

frequently closes the history. A considerable number of pellagrous individuals end their sufferings by suicide.

The fact that this disease exists practically only in epidemic form renders its diagnosis easy.

The most characteristic post-mortem findings may be stated as follows: The body is greatly emaciated, the intestinal walls are very thin on account of the wasting away of the muscular coat, ulceration in the intestines is frequently found, the cells of the liver and of the spleen and the muscles of the heart are deeply pigmented. Atrophy seems to be most marked in those organs connected with the vagus nerve, the lungs, heart, kidneys, spleen, and intestines. Although marked alterations from the normal are frequently found in the brain and cord, there seems to be no constant or characteristic lesion.

Treatment.—As is true of all epidemics of food poisoning prophylactic measures are the most effective. As has already been stated, Indian corn, properly cultivated, harvested, and cooked, is not only a safe but a valuable food, and the existence of such a disease as pellagra is not only a national calamity but a national disgrace. If communities be so poor that they must live on decomposed food the state should relieve their poverty; if they be so ignorant that they poison themselves, the state should instruct them. Maize, which is better suited to the soil and climate, should be selected for seed or other grains should be introduced in order that the food should not be so largely confined to corn. Intelligent men should supervise the harvesting, the storing, the grinding, and if need be the cooking. The Spanish have given to this disease its most appropriate name, "mal de la miseria."

There is no medicinal specific for the disease. Many of the milder cases recover when the patients are placed under proper hygienic conditions and supplied with proper food. In its advanced stages pellagra is practically an incurable disease. It can be treated only symptomatically. For the intestinal disturbances calomel and bismuth subnitrate are favorite prescriptions. The persistent diarrhœa is ordinarily treated with opiates and astringents. For the paralytic symptoms Lombroso prescribes arsenic in the form of Fowler's solution, beginning with five drops and gradually increasing to thirty at a dose. The same authority recommends for the vertigo the tincture of cocculus orientalis. This is given in doses of from three to five drops. All kinds of tonics such as iron, quinine, and strychnine in their various forms of administration have been used, and possibly they may be of benefit in the less advanced stages of the disease.

THE POISONS OF THE SPECIFIC INFECTIOUS DISEASES.

We will now give a brief statement of the more important products of the specific pathogenic bacteria. However, before taking up the individual infectious diseases, it might be well to give some attention to the general effects on the body of bacterial poisons. In doing this we will consider in the first place the action of bacterial poisons upon the temperature of the body. Do all bacteria induce fever? Are all animals alike affected in this respect by the different bacteria? Is there any relation between the fever-producing properties of a given germ in a given animal and its pathogenic action upon that animal? These are questions which Krehl has attempted to answer experimentally. The germs employed by him were bacillus pyocyaneus, b. coli, b. anthracis, b. typhi abdominalis, b. diphtheriæ, b. choleræ, b. proteus, b. subtilis, b. prodigiosus, and b. Metchnikovi. The animals experimented upon were cats, dogs, rabbits, guinea-pigs, pigeons, chickens, and a hedgehog. The bacteria were grown on agar or potato for two or three days, then were removed, suspended in sterilized water, and boiled. In the pigeons, chickens, and hedgehog no elevation of temperature could be induced by these dead bacteria. In the pigeons the temperature was generally lowered. Rabbits were found to be specially susceptible, dogs were less easily affected, only five of the above-mentioned germs causing an elevation of temperature in these animals. Different germs acted differently upon guinea-pigs, but as a rule small doses elevated, while larger doses depressed the temperature. There was found to be no constant relation between the fever-inducing and the pathogenic properties of the bacteria. Boiled diphtheria bacilli had practically no effect upon the temperature of guinea-pigs, rabbits, and dogs, while the bacillus subtilis, which is wholly devoid of pathogenic properties, markedly elevated the temperature of dogs. These experiments are open to the objection that the fever-inducing substances contained within the bacterial cells may have been destroyed by the heat employed in the boiling. Moreover, too much must not be ascribed to the action of the bacteria, since other substances may markedly elevate the temperature when given subcutaneously. Certain enzymes, such as pepsin, diastase, rennet, etc., boiled or unboiled, when administered subcutaneously cause an elevation of temperature in rabbits, guinea-pigs, and dogs. Sterilized beef tea causes a distinct elevation of temperature in guinea-pigs. Five-per-cent. sterilized solutions of sodium nitrate, chloride, iodide, and bromide, when given

hypodermically, cause fever in rabbits. It has been found that the temperature of tuberculous animals is more easily affected by bacterial products in general than that of healthy animals. Paralactic acid is said to have, so far as its effect upon the temperature is concerned, an action very similar to that of tuberculin. Not only does this acid elevate the temperature, but the tuberculous areas are observed to become hyperæmic and in some hemorrhagic spots may be found. Doses of from 0.3 to 1 gm. of deuteroalbumose injected under the skin of healthy guinea-pigs cause an elevation of temperature without more serious effects, while like doses administered to tuberculous guinea-pigs may cause death. If section be made of these animals, inflammatory areas will be found about the tuberculous lesions identical with those caused by tuberculin.

Anthrax.

It must be admitted that for a disease so speedily fatal as anthrax we should expect to find its specific bacterium elaborating a more powerful poison than any that has yet been obtained. However, since the germ grows so abundantly and is so widely distributed in the body, it is not necessary that any individual bacterial cell should contain a large amount of poison. In other words, the large number of germs may make up for the lack of virulence of the chemical poison. Both ptomaïns and toxins have been found in cultures of the anthrax germ. The first successful attempt to study the chemical poisons of anthrax was made by Hoffa, who obtained from pure cultures of the cells small quantities of a ptomaïn which when injected under the skin of animals produced the symptoms of the disease and death. Hoffa named this poison anthracin. Later, he has obtained the same poison from the bodies of animals dead with anthrax. These results cannot be considered as altogether satisfactory. It is possible that the basic substance obtained by Hoffa is not a constant product of the growth of the anthrax bacillus. It is at least certain that many other investigators have failed to confirm Hoffa's work. In 1889 Hankin prepared from cultures of the anthrax bacillus an albumose which when employed in comparatively large amount proved fatal to animals, but when used in small quantity gave immunity against subsequent inoculation with the living germ. This substance was not obtained in a chemically pure condition, and we are ignorant of the amount of it necessary to cause death. Brieger and Fraenkel obtained a so-called toxalbumin of anthrax from animals in which the disease had been induced by inoculation with the bacillus. The liver, spleen, lungs, and kidneys of these animals

were finely divided and rubbed up with water. After this mixture had stood in a refrigerator for twelve hours, it was passed through a porcelain filter and the proteid was precipitated from the filtrate with absolute alcohol. Martin, by growing the anthrax bacillus for from ten to fifteen days in an alkaline albuminate from blood serum, and then by filtration through porcelain, has obtained the following products:

1. Protalbumose and deuteroalbumose and a trace of peptone. All of these react chemically like similar substances prepared by peptic digestion; 2. An alkaloid; 3. Small quantities of leucin and tyrosin.

The mixed albumoses are poisons only in considerable doses, as much as 0.3 gm. being required to kill a mouse weighing 22 gm. when injected subcutaneously. Smaller doses cause œdema and a somnolent condition from which the animal recovers. The alkaloid causes similar symptoms to those induced by the albumoses. It is, however, more poisonous and acts more rapidly than the albumoses. The animal is affected immediately after the injection and falls into a comatose condition, which terminates in death. The alkaloid produces œdema and in many cases thrombi in the small veins. Extravasation into the peritoneal cavity is occasionally seen, and the spleen is often enlarged and filled with blood. The fatal dose of the alkaloid for a mouse is from 0.1 to 0.15 gm. With these amounts, death results within three hours. This alkaloid obtained by Martin is not identical in its action with the anthracin of Hoffa.

Marmier has studied the chemical substances formed by the growth of the anthrax bacillus in solutions of peptone. From these cultures he has obtained a toxin which is soluble in water, insoluble in chloroform, ether, and absolute alcohol. It does not give any of the reactions of the albuminoids, albumoses, peptones, or alkaloids. There is no proof that this toxin was obtained in the pure state. The author's conclusions are as follows:

1. A specific toxin may be extracted from glycerin-peptone cultures of the anthrax bacillus.

2. This toxin does not give the reactions of albuminoid substances. It does not change starch, sugar, or glycogen.

3. Animals (chickens, frogs, fish) that are immune to the anthrax bacillus are also indifferent to the toxin. Similar results were observed in rabbits artificially immunized with attenuated cultures.

4. This toxin is attenuated but not destroyed by boiling at 110° C., thus differing from the venom of serpents, the toxins of diphtheria and tetanus, and the enzymes.

5. On the contrary, like the other bacterial toxins it loses its

action on animals after being brought in contact with the alkaline hypochlorites. Prolonged insolation in the presence of air leads to the same result.

6. By employing carefully graduated doses of this toxin it is possible to immunize animals to the anthrax bacillus in the same way as other specific toxins give immunity to the corresponding diseases.

7. Anthrax cultures in other fluids such as blood serum and bouillon from the flesh of the horse, ox, or calf do not contain this toxin in appreciable quantities.

8. On the contrary, one may extract a toxin from anthrax cultures on nutritive gelatin by macerating the microbes in dilute alcohol.

9. The toxin is contained within the bacterial cells, and in order to obtain it in a culture there must be opportunity for it to diffuse from the cells.

Whether the toxin as obtained by Marmier was chemically pure or not, there can be but little doubt that he was dealing with the specific poison of anthrax. The symptoms induced by this toxin are identical with those observed in the same animals after infection with the anthrax bacillus.

Asiatic Cholera.

Without any experimental evidence it might have been predicted that the cholera bacillus produces soluble chemical poisons. In this disease the germ is not distributed through the body, but is practically confined to the intestines. Notwithstanding this fact the central nervous system is markedly affected, showing the action of some substance circulating in the blood. Experimentation has confirmed these theoretical considerations, and it has been demonstrated that the cholera bacillus is one of the most active chemically of the pathogenic germs.

As early as 1846 Virchow observed that a red coloration appeared on the addition of nitric acid to filtered cholera stools. Again, in 1885, Griesinger noticed this coloration on the addition of nitric acid to rice-water stools. Bujwid was the first to call attention to this cholera reaction when nitric acid is added to cultures of Koch's comma bacillus. Brieger demonstrated that this coloration is due to an indol derivative, and he obtained indol by the distillation of cholera cultures which had been acidified with acetic acid. This formation of red color on the addition of nitric acid to cholera cultures is now known as "the cholera reaction," and for some time it was believed to be characteristic of this bacillus. However, we now know that there are many germs which produce indol, and in whose cultures

this reaction can be obtained. From Petri's study of the indol reaction, the following conclusions may be given:

1. Seven pure cultures of the cholera germ from as many sources gave the reaction with equal distinctness.

2. Of one hundred other bacteria tested in the same way, twenty gave a red coloration. In nineteen of these the coloration is due to the nitroso-indol reaction of Bayer. The twentieth bacillus, which was that of anthrax, gave a red coloration which was not due to indol.

3. In case of the cholera germ and the other bacilli the action is due to the reducing effect of the bacteria on nitrates. The reaction is most marked with the cholera bacillus at blood temperature.

4. None of these bacteria convert ammonia into nitrate.

5. The addition of sulphuric acid alone is sufficient to give the test, which, however, is most marked when the solution contains 0.01 per cent. of nitrite.

6. The reaction is more marked if the sulphuric acid be added after the addition of a very dilute nitrite solution.

Brieger has also prepared a "cholera blue" from cultures of the cholera germ in meat extract containing peptone and gelatin. This substance, which is yellow by reflected and blue by transmitted light, is developed on the addition of concentrated sulphuric acid to the culture. If the culture be treated with sulphuric acid, then rendered alkaline with sodium hydrate and extracted with ether and the ether evaporated, "the cholera red" may be dissolved from the residue with benzol, leaving the "cholera blue" which may now be dissolved with ether. "Cholera blue" gives characteristic absorption bands which appear between E and F.

The cholera bacillus produces in meat-peptone cultures a peptonizing ferment which remains active after the germ has been destroyed. This ferment resembles pancreatin, inasmuch as it is more active in alkaline than in acid solutions. The resemblance to pancreatin is still further shown by the fact that the activity of the ferment is increased by the presence of sodium carbonate or sodium salicylate. The method of preparing this ferment has already been given (see page 7). It is possible that the destructive changes observed in the intestines in cholera are in part due to the action of this ferment.

There is also a diastatic ferment produced in cholera cultures. All attempts to isolate this ferment have been unsuccessful. Its presence can be recognized only by its action on starch. It resembles ptyalin not only by its action upon starch, but by the fact that it is destroyed by a temperature of 60° C.

Cantani was one of the first to demonstrate the presence of chemical poisons in cultures of the comma bacillus. He injected

sterilized cultures of this germ into the peritoneal cavity in small dogs and found that after from fifteen to thirty minutes the following symptoms appeared: Great weakness, tremor of the muscles, drooping of the head, prostration, convulsive contractions of the posterior extremities, repeated vomiting, and cold head and extremities. These symptoms gradually abated and after twenty-four hours recovery seemed to be complete. The cultures employed by Cantani were three days old when sterilized. He found that when a high temperature was used in sterilization the toxicity of the cultures was markedly decreased. He concluded from this that the poisonous substance is volatile, but the effect of great or prolonged heat in diminishing the toxicity was more probably due to its destructive effect on the toxin. The same observer reports that the blood of those sick with cholera may be acid. This finding has been confirmed by Strauss, who examined the blood of cholera patients immediately after death. Ahrend has found lactic acid in the urine of cholera patients.

Nicati and Rietsch removed the bacilli from cholera cultures by filtration through porcelain, and injected the filtrate intravenously into animals. When thus used these cultures acted fatally on dogs. This demonstration of the poisonous properties of filtered cholera cultures has been confirmed by Ermengem and others. Klebs made cultures of the cholera bacillus on preparations of fish. These cultures were acidified, filtered, the filtrate evaporated on the water-bath, and the residue taken up with alcohol and precipitated with platinum chloride. The platinum was removed from this precipitate by hydrogen sulphide, and the crystalline residue obtained on evaporation of the filtrate was dissolved in water and injected intravenously into rabbits. These animals manifested marked muscular contractions, but it did not cause death except when in addition to this extract unsterilized cultures were injected. In the animals killed by these injections, Klebs found an extensive calcification of the epithelium of the uriniferous tubules. This investigator believes that the change in the kidney is induced by the chemical poison, and from this standpoint he explains the symptoms of cholera as follows: The cyanosis is a consequence of arterial contraction which is the first effect of the poison. The muscular contractions also result from the action of the chemical poison. The serous exudate into the intestine follows upon epithelial necrosis. Suppression of urine and subsequent symptoms appear when the formation and absorption of the poison becomes greatest.

By the Stas-Otto method, Villiers obtained from the bodies of two persons dead from cholera a poisonous base which was liquid, pungent to the taste, and possessed of the odor of hawthorne. This base

was strongly alkaline in reaction, and gave precipitates with the general alkaloidal reagents. When injected into frogs in doses of from 1 to 2 mgm. it decreased the activity of the heart, caused violent trembling, and death. The heart was found to be in diastole and filled with blood, and the brain slightly congested. It should be stated, however, that the presence of this substance in the bodies of persons who had died of cholera does not prove that it is a product of the growth of the cholera bacillus. Similar substances have been found in the bodies of persons dead from other diseases, and they are to be regarded as frequent products of putrefactive changes.

An oily base was obtained from cholera stools by Pouchet. The stools were extracted with chloroform, and the base was believed to belong to the pyridin series. It reduced ferric, gold, and platinum salts, and formed an easily decomposable hydrochloride. It was a violent poison, causing irritation of the stomach and retarding the action of the heart. Subsequently the same investigator obtained an apparently identical substance from cultures of the comma bacillus.

Brieger has studied cholera cultures by his well-known method of isolating ptomaïns. He employed pure cultures of the cholera germ on beef broth which had been rendered alkaline by the addition of a three-per-cent. soda solution. These cultures were kept in the incubator at from 37° to 38° C. and tested from time to time. After twenty-four hours cadaverin was found to be present. Older cultures yielded small quantities of putrescin. The last-mentioned base, however, was found to be much more abundant in blood-serum cultures than in those of beef broth. Cadaverin and putrescin were formerly supposed to be inert, but it is now known that they cause necrosis of tissue with which they come in contact, and it is possible that the necrotic changes observed in the intestines after death from cholera may be due to the action of these bases. The lecithin in the above-mentioned broth was slowly acted upon by the cholera germ, but with increasing age the amount of cholin in the culture increased, reaching its maximum during the fourth week. Kreatin resisted for some time the action of the cholera bacillus, but after six weeks a considerable quantity of kreatinin and a similar amount of methyl guanidin were isolated. The last-mentioned substance is highly poisonous, causing muscular tremors and dyspnœa. The presence of methyl guanidin in cholera cultures is supposed to indicate that the comma bacillus acts as an oxidizing agent, since kreatinin yields methyl guanidin only by oxidation. In addition to the above-mentioned ptomaïns, Brieger succeeded by his method in obtaining from cholera cultures two poisons which he at that time considered specific products of this germ. One of these is a diamin, and is found in

the mercuric-chloride precipitate. It produces muscular tremor and cramps. In the mercury filtrate there was found another poison which in mice induced a lethargic condition. The respiration and the action of the heart became slow, the temperature sank so that the animal felt cold to the touch, and in some there was a bloody diarrhœa. It is possible that some or all of these substances found by Brieger may be artificial products formed during the process of extraction. Whether this be true or not, it is quite certain that they are not prominent factors in the production of the symptoms of cholera.

In their studies of the toxalbumins Brieger and Fraenkel obtained an insoluble proteid from cultures of the cholera bacillus. This substance when suspended in water and injected subcutaneously in guinea-pigs caused death after from two to three days. Section showed redness of the subcutaneous tissue and an inflammatory swelling extending into the muscle for some distance about the point of injection, but there was no necrosis. In some of the animals there was evidence of beginning fatty degeneration of the liver.

In his study of the methods of inducing immunity from cholera, Gamaleïa treated animals with cholera cultures sterilized at 120° C. Subcutaneous injections of these sterilized cultures caused transient œdema from which the animal soon recovered. However, when he employed cultures sterilized at 60° C., large doses caused death in rabbits when injected intravenously. The animals refused food, and a persistent diarrhœa appeared. The urine became albuminous, and in some instances there was retention of this secretion.

Petri studied the chemistry of cultures of the cholera bacillus in peptone. In such cultures he found large quantities of tyrosin, leucin, a small quantity of indol, fatty acids, poisonous bases, and a poisonous proteid. This proteid resembled peptone in its behavior towards chemical reagents, and it was designated by Petri as toxipeptone. In quantities of 0.36 gm. per kilogram body weight and in larger quantities it proved fatal to guinea-pigs in eighteen hours. It produced muscular tremor and paralysis. Post-mortem examination showed an effusion into the peritoneal cavity, marked injection of the blood-vessels of the intestines, and isolated hemorrhagic spots. This proteid was not rendered inert by a temperature of 100° C. It is not to be regarded as a chemically pure substance, but was undoubtedly contaminated with more or less unchanged peptone.

Scholl studied the products obtained by the growth of the cholera germ in sterilized eggs. Fresh eggs were sterilized and inoculated in the usual way. After having been kept for eighteen days they were opened and the contents examined. The white of the egg was found to be completely fluid, and to give off a strong odor of hydrogen sul-

phide. Five cubic centimetres of the fluid contents of one of these eggs were injected into the abdomen of a guinea-pig. Soon the posterior extremities were paralyzed, and after ten minutes the paralysis became general. After five minutes more, convulsive movements of the extremities began, and forty minutes after the injection the animal was dead. Section showed the vessels of the small intestine and stomach highly congested, a colorless effusion in the peritoneal cavity, and the heart in diastole. It is altogether probable that these effects were due to the hydrogen sulphide, as practically the same symptoms may be induced in guinea-pigs by similar treatment with aqueous solutions of this substance. However, that there was present a poisonous substance in addition to the hydrogen sulphide was demonstrated by Scholl in the following manner: The albuminous content of the egg was poured into ten times its volume of absolute alcohol. The precipitate which formed was collected and washed with alcohol until the filtrate became colorless. The washed precipitate was then digested for fifteen minutes with 200 c.c. of water and filtered; 8 c.c. of this filtrate was injected into the abdomen of a guinea-pig. Paralysis resulted immediately, and within one and one-fourth minutes the animal was dead. This impure toxin was rendered inert by a temperature of 100° C. It was not altered by short exposure to 75°, but attempts to evaporate the solution at 40° in vacuo destroyed its poisonous properties.

Hueppe claims that the cholera poison results from the ferment action of the germ on the proteid in which it occurs, and that the proteid of the bacterial cell is not poisonous. He believes that the proteid of the bacterial cell is the immunizing substance present in cholera cultures. He claims that the toxin and the immunizing substance can be separated in the following manner: Rice-water stools from cholera patients are treated with absolute alcohol. Both the toxic and the immunizing substances are precipitated. By collecting this precipitate and extracting it with sterilized water or physiological salt solution the toxin only is dissolved. Hueppe claims that in a given case of cholera the toxin may form most abundantly and the immunizing substance only in small amount. In such cases the symptoms of the disease would be violent, and should recovery occur the immunity to subsequent infection would be slight. With the conditions reversed the disease might be slight and the immunity established great.

There are two theories as to the mode of formation of the toxin of cholera. Pfeiffer holds that the poison is a constituent of the germ cell and that it is not set free until the germ dies and disintegrates. On the other hand, Metchnikoff believes that the toxin is a soluble

secretion formed in the cell, and constantly given off from the same. The latter view is apparently demonstrated by some recent experiments by Metchnikoff and Roux.

Tetanus.

Brieger obtained from mixed cultures of the tetanus germ four poisonous substances. The first of these, tetanin, which rapidly decomposes in acid solutions, but is stable in alkaline solutions, produces tetanus in mice when injected in quantities of only a few milligrams. The second, tetanotoxin, produces first tremor, then paralysis, followed by convulsions. The third, to which no name has been given, causes tetanus accompanied with a free flow of the saliva and tears. The fourth, spasmotoxin, induces clonic and tonic convulsions. The same experimenter isolated tetanin from the amputated arm of a man with tetanus, thus showing that this chemical poison is formed in the body as well as in artificial cultures. More recent researches have shown us that these crystalline bodies obtained by Brieger do not constitute the most active poisons produced by the tetanus bacillus.

Brieger and Cohn have prepared tetanus toxin from cultures of the bacillus in veal broth containing one per cent. of peptone and one-half per cent. of common salt. These cultures were rendered germ free by filtration through porcelain and treated with ammonium sulphate to supersaturation. This reagent throws the poison out of solution and it floats on the surface from which it is removed with a platinum spatula. This crude poison when dried in vacuo is found to contain 6.5 per cent. of ammonium sulphate. Of the filtered culture 0.00005 c.c. suffices to kill mice. From one litre of the culture 1 gm. of the dry substance was obtained, and of this 0.0000001 gm. killed a mouse with the typical symptoms of tetanus. This crude product contains besides the poison, albumins, peptone, amido-acids, volatile substances, and ammonium sulphate with other salts. The albumin was removed by precipitation with basic lead acetate. The peptone, amido-acids, and salts were removed by dialysis, and finally, evaporation in vacuo at from 20° to 22° C. removed the volatile substances. The toxin thus obtained is yellow, flocculent, readily soluble in water, odorless, and similar to gum arabic in taste. It turns polarized light slightly to the left, it fails to give the Millon and xanthoproteid reactions, but does give with copper sulphate and caustic potash a faint violet coloration, not identical with the rose tint of the biuret reaction. With the exception of ammonium sulphate, the metallic salts such as sodium chloride and sulphate, magnesium sulphate, potassium nitrate, mercuric chloride, and potassium

ferrocyanide with acetic acid, failed to precipitate the poison. Moreover, calcium phosphate, which Roux and Yersin used for carrying down the diphtheria poison, also magnesium carbonate and aluminum hydrate, do not precipitate the tetanus poison. This poison contains no phosphorus and only unweighable traces of sulphur. Of the best preparation obtained at that time by these investigators 0.00000005 gm. killed a mouse of 15 gm. weight. The authors figure from this that the fatal dose for a man of 70 kgm. weight would be 0.00023 gm., or 0.23 mgm., and that 0.04 mgm. would induce symptoms of tetanus. The smallest fatal dose of atropine for the adult is 130 mgm., and of strychnine from 30 to 100 mgm. "From this one can judge of the fearful weapons possessed by the bacteria in their poisons."

Fermi and Pernossi reach the following conclusions from their studies of the tetanus poison:

1. First, agar cultures are the most poisonous, next come those on gelatin, and lastly, those in bouillon.

2. Chickens, turtles, snakes, and tritons are immune to the poison.

3. In the above-mentioned animals the tetanus poison may remain and retain its virulence for three days or even longer.

4. Filtrates from agar and gelatin cultures are more resistant to heat than those from bouillon. Like the enzymes, the purer the tetanus poison the less stability does it possess.

5. Dissolved in water the tetanus poison is rendered inert by a temperature of 55° C., but in the dry state it can be heated to 120° C. without loss of virulence.

6. When the dried poison is mixed with ether or chloroform and heated to 80° C. it is destroyed, but with amylic alcohol or benzol a temperature of 100° C. is required to accomplish this result.

7. Dissolved in water this poison is destroyed by direct sunlight after an exposure of eight to ten hours (with the highest temperature on a blackened thermometer at 56° C.) or after fifteen hours when the temperature did not exceed 37° C.

8. In the dry state the tetanus poison can be exposed to the direct sunlight for one hundred hours without loss of virulence.

9. Under the action of an electric current of 0.5 ampère continued for two hours the substance becomes inert.

10. The poison is destroyed by the following substances: Potassium permanganate, 50 per cent. for forty-eight hours; phosphotungstic acid, saturated solution, for twenty-four hours; lime water, saturated solution, for twenty-four hours; aseptol, concentrated, for twenty-four hours; lysol concentrated, for twenty-four hours; hydro-

chloric acid, 25 per cent., for twenty-four hours; butyric acid, 25 per cent., for twenty-four hours; phosphoric acid, 25 per cent., for twenty-four hours; oxalic acid, 4 per cent., for twenty-four hours; tartaric acid, 1 per cent, for twenty-four hours. It is not destroyed by the following: Antimony tartrate, 5 per cent., twenty-four hours; lead acetate, four days; magnesium oxide, forty-eight hours; chloroform, four days; acetic acid, twenty-four hours.

According to Kitasato the tetanus poison is destroyed after twenty-four hours' exposure to the following: Tannin, 1.5-per-cent. solution; caustic lime, 0.08 per cent.; paraphenol-sulphuric acid, 2.5 per cent.; ammonia, 6.9 per cent.; caustic soda, 3.2 per cent.; barium hydrate, 1 per cent.; platinum chloride, 0.4 per cent. After an exposure of one hour: Gold chloride, 0.5 per cent.; alcohol, 60 per cent.; methyl alcohol, 50 per cent.; amyl alcohol, 77 per cent.; carbolic acid, 1.5 per cent.; soda lye, 0.4 per cent.; iodine trichloride, 0.5 per cent.; kreosol, 1 per cent.

11. Sulphuric oxide, oxygen, carbonic acid, carbon monoxide, methane, and hydrogen, even after from ten to fifteen hours, do not appreciably impair the poison.

12. Gastric juice destroys the poison through the activity of the hydrochloric acid, and not by virtue of the pepsin.

13. Ptyalin, diastase, and emulsin have no action. The effect of trypsin has not been satisfactorily determined.

14. Putrefactive germs do not destroy the poison.

15. The living but not the dead intestines of guinea-pigs and cats destroy the poison.

16. The living intestine of the chick does not destroy and does not absorb the poison.

17. The poison may be eliminated by the kidneys and retain its properties in the urine.

18. The poison is not a ferment.

Bruschettini has studied the distribution of the tetanus poison in the body and its elimination, in the following manner: Animals were poisoned by injections of the toxin. When death from the poison was imminent they were killed and pieces of various organs rubbed up with sterilized water were injected into other animals. The preparations from the liver and suprarenal capsules were invariably without effect, while those from the kidney were constantly poisonous. This was supposed to demonstrate that the poison is eliminated by the kidney. The blood taken from the vena cava was found to be poisonous in three out of four experiments. When the injections of the toxin were made under the skin, the lumbar cord was found to be active in four out of eight cases, and in all when the injections were made

directly into the sciatic nerve. On the other hand, when the inoculations were made under the dura mater, the brain was found to be active and the lumbar cord remained inactive. From these experiments it is concluded that the poison not only circulates in the blood, but is deposited in the central nervous system. This author has also found the toxin in the urine of men suffering from tetanus. However, Bruner in several cases of tetanus in man, Stern in two, and Brieger in one case, were not able to induce tetanus in animals by injecting into them even large doses of the urine of patients with this disease. This only shows that the poison is not in all cases eliminated by the kidney in sufficient quantity to render the urine highly toxic. In a fatal case of acute tetanus Vulpius failed to induce tetanus with the urine voided during life, but succeeded with that found in the bladder after death.

Buschke and Oergel induced tetanus in guinea-pigs with blood serum obtained by venesection from a fatal case of this disease. With extracts from the liver, spleen, and spinal cord after death like results were also obtained in mice. According to the studies of Quadu the tetanus poison when injected directly into the blood circulates unchanged and unabsorbed for some hours. He states that a much larger dose is required to induce symptoms when given intravenously than when given subcutaneously.

Liermann found that material taken from the arm of a man who had died from tetanus, and who had been buried for two and one-half years, induced tetanus in animals. This would seem to indicate that the poison retains its virulence for a long time. In this material there were found nine kinds of bacteria, but none of these in pure or in mixed cultures induced tetanus. This author explains these findings by supposing that non-pathogenic bacteria may receive toxicogenic properties from the media in which they grow. With the tetanus bacillus widely distributed in the soil it would not be surprising to find that material taken from the arm of a man dead from any disease after burial for two and one-half years should induce tetanus in animals. Moreover, the failure to find the tetanus bacillus does not call for the supposition given by Liermann. The tetanus poison without any bacilli would produce the same effect.

Many attempts have been made to find in other germs or in other products some agent which would neutralize the tetanus poison. Roncali, with this in view, has tested forty different germs. His results were wholly negative. The tetanus poison was found to act more energetically in animals inoculated with certain other bacteria or treated with other products, and in no case was there any evidence of antagonism in action.

Diphtheria.

The fact that the bacillus of this disease, although found only at the place of inoculation, causes marked systemic disturbances indicates that its action must be due to its soluble products. This was early recognized by the discoverer of the bacillus, Loeffler, who in 1887 attempted to ascertain the nature of the poison. A flask of bouillon containing peptone and grape sugar was, three days after it had been inoculated with the bacillus, evaporated to 10 c.c., and this was injected into an animal, but was without effect. A second flask of the same material was extracted with ether, but this extract was also found to be inert. Some neutral beef broth was extracted with glycerin some four or five days after it had been inoculated with the bacillus. The glycerin extract when treated with five times its volume of absolute alcohol deposited a voluminous flocculent precipitate which was collected, washed with alcohol, dried, and dissolved in a little water. It was again precipitated with alcohol and a current of carbonic-acid gas. By this means there was obtained a white substance, and from 0.1 to 0.2 gm. of this dissolved in water and injected subcutaneously in guinea-pigs caused marked pain followed by œdema terminating in necrosis.

Roux and Yersin studied diphtheria cultures which had been freed from the bacillus by filtration through porcelain tubes. Animals were inoculated with these filtered cultures. The results obtained varied with the amount of the fluid, the species of the animal, and the method of administration. In general the effects observed were a serous exudate in the pleural cavity, an acute inflammation of the kidney, fatty degeneration of the liver, and an œdematous swelling in the surrounding tissue after subcutaneous inoculation. In some animals paralysis, generally in the posterior extremities, resulted. The action of this poison was found to be very slow, and as a rule death occurred days and in some instances weeks after the inoculation, and was generally preceded by marked emaciation. These investigators at first employed cultures seven days old. Later they worked with cultures six weeks old, and these were found to contain larger amounts of the poison. In such cultures after filtration the poison was present in such quantities that from 0.2 to 2 c.c. injected under the skin in guinea-pigs induced the above-mentioned symptoms. It was found that when these filtered cultures were heated to 100° C. for twenty minutes they were rendered inert, and that a temperature of 58° C. maintained for two hours markedly lessened their virulence. Roux and Yersin ascertained

that the poisonous substance could be carried down mechanically from cultures on the addition of calcium chloride. The great toxicity of this precipitate is indicated by the statement that 0.4 mgm. suffices to kill eight guinea-pigs or two rabbits, and that 2 cgm. containing about 0.2 mgm. of the pure poison killed a guinea-pig within four days. Roux and Yersin as well as Loeffler came to the conclusion that the diphtheria poison is a ferment.

In their early studies of the diphtheria poison Brieger and Fraenkel employed two methods of sterilizing their cultures. In the first method the bacilli were destroyed by heat. They ascertained that a temperature of 100° C. rendered the cultures inert, but that a temperature of 50° C. was sufficient to destroy the germs, while the virulence of the chemical products was not affected. The second method consisted of removing the bacteria by filtration through porcelain. The germ-free filtrate could be heated to 50° C. without loss of toxicity, while a temperature of 60° C. rendered it inert. Varying quantities of filtered cultures were used upon animals, mice, guinea-pigs, and rabbits, and it was found that the effects varied with the quantities employed and the methods of administration. The symptoms appeared most promptly when the injections were made intravenously. In all cases in which death did not occur too early paralysis appeared. The limbs were first affected, and this was true whether the fluid was administered intravenously or subcutaneously. The post-mortem appearances were identical with those observed after inoculation with the bacillus with the exception of the absence of the pseudomembrane. After subcutaneous injection there was a gelatinous grayish-white, sometimes reddish, œdematous fluid formed at the point of injection, and after larger doses there was necrosis of tissue. In cases in which death was delayed there were effusions in the pleura, fatty degeneration of the liver, and inflammation of the kidneys.

Tangl has shown that the chemical poison of diphtheria is formed in the body as well as in culture flasks. A large piece of pseudomembrane was macerated in water in an ice chest for twenty-four hours and then filtered through porcelain. The filtrate injected into animals produced all the symptoms that had been obtained by the similar employment of artificial cultures. The same observer noticed that in some animals inoculated with the sterilized cultures through the mucous membrane a pseudomembrane formed at the point of injection. The diphtheria poison has also been found in the tissues, blood, and urine.

Kossel has shown that the specific toxin of diphtheria is a secretion of the bacterial cell. Its formation begins with the growth of the

bacilli, and it appears in cultures before the cells begin to break down and before their contents pass into solution. When the bacilli die the production of the poison ceases. In this way we understand that the exaltation of diphtheria bacilli consists of a development of their specific function.

Schierbeck states that the production of toxin by the diphtheria bacillus is favored by the presence of free carbonic acid, and he recommends that in the preparation of the toxin the diphtheria cultures be treated with a current of air containing eight per cent. of this gas.

Smirnow states that the globulin of the normal blood serum of the horse neutralizes the diphtheria poison. Dieudonné has tested the action of globulin obtained from blood serum by different methods. Two methods were finally adopted and these consisted (1) in precipitation by saturation with magnesium sulphate, and (2) in treatment with a current of carbonic-acid gas. The globulin obtained by the first-mentioned method markedly neutralized the diphtheria poison, while the other preparation had but little effect. This would seem to indicate that the neutralizing action is not due to the globulin, but to some substance carried down by this proteid.

According to Sprouck the most active diphtheria toxin is formed when the bacillus is grown upon bouillon prepared from meat several days old, and in which the sugar has undergone fermentative decomposition. The peptone used in the preparation of culture media should also be free from sugar.

Dungers has shown that the diphtheria bacillus produces more toxin when grown in culture media containing ascitic fluid from man than it does in ordinary culture media.

Dzierzgowski and Rekowski have made the following study of the chemical products of the diphtheria bacillus. In the first experiment, four flasks each containing two litres of a solution of commercial peptone in water was employed. After sterilization, two flasks were inoculated with the bacillus, while the other two were kept as controls. All of these flasks stood for six weeks at a temperature of 36.5° C. Then the contents of one diphtheria and one control flask were distilled separately to half the volume, and the distillates redistilled and evaporated. Then these residues were freed from ammonium chloride with absolute alcohol, that from the inoculated flask left a substance soluble in water and fatal to a rabbit in fifteen minutes, while that from the control flask had no poisonous properties. The albumose precipitated by absolute alcohol in both flasks gave substantially the same chemical reactions, but that from the inoculated flask in doses of 0.2 gm. administered subcutaneously

killed guinea-pigs, while that from the other flask in double this amount had no effect. The substances soluble in alcohol from both flasks were not poisonous. Attempts were made to obtain the volatile body in large amount and chemically pure but without success. In the purest form obtained 0.15 gm. sufficed to kill a guinea-pig within eight minutes.

Typhoid Fever.

Brieger has obtained from pure cultures of the Eberth bacillus a poisonous base which causes in guinea-pigs a slight flow of saliva, increases the frequency of respiration, dilates the pupils, induces profuse diarrhœa, and leads to paralysis followed by death within from twenty-four to forty-eight hours. Post-mortem examination of these animals shows the heart to be in systole, the lungs hyperæmic, and the intestines contracted and pale. For a while this poison was regarded as the specific product of the typhoid bacillus, and Brieger named it typhotoxin. Later Brieger and Fraenkel obtained from pure cultures of the Eberth bacillus a proteid which causes death in rabbits after from eight to ten days. Pfeiffer has shown that the poison is contained in the bacterial cells. From 3 to 4 mgm. of this substance for each 100 gm. of body weight suffice to kill guinea-pigs. With this poison animals can be rendered immune to Eberth's bacillus, but not to the bacillus coli communis.

In 1889 the writer obtained from mixed cultures from typhoid stools a base, forming crystalline salts and capable of inducing in cats and dogs a marked elevation of temperature accompanied by severe purging. The following is a record of one experiment with this substance: "An aqueous solution of the crystals was given to a dog by the mouth at 3 P.M. The rectal temperature before the administration was 101° F. At 3:15 purging and vomiting set in and continued at intervals for more than two hours. At 3:30 the temperature was 103° F. At 3:55 the animal began to purge. The first discharges contained much fecal matter, but subsequently they became watery and contained mucus stained with blood. At 4:00 the temperature was 103.5° F., and remained at the same point at 4:30. The animal was not seen again until 10:00 A.M. the next day, when its temperature was 100.5° F., and recovery seemed complete." This base was not obtained in quantities sufficient for an ultimate analysis. The platinochloride crystallizes in fine rhombic prisms and the hydrochloride in long, delicate red needles. The red color seems to be inherent to the substance and not due to impurities. The mercury and platinum compounds are insoluble in alcohol, but

soluble in water. The hydrochloride is soluble in both water and alcohol.

It has been claimed by Rodet and Roux of Lyons that the bacillus coli communis and the typhoid bacillus are varieties of the same species. If this be true, the pollution of drinking-water with normal fæces may cause typhoid fever. It is, therefore, evident that a positive decision on this point is of great importance. Attempts to reach such a decision were first made by rendering animals immune to one of these germs, and then ascertaining whether or not this immunity holds good against the other. The results reached by experiments of this kind were contradictory. Sanarelli and Demell and Orlandi found that animals immunized against the typhoid bacillus were also immune to the colon bacterium, and those protected in like manner against the latter became immune to the former. These investigators reach the conclusion that the products of these germs are biologically equivalent. On the other hand, Neisser found that animals protected against from twelve to twenty times the ordinarily fatal dose of the typhoid bacillus died when treated with from two to three times the usually fatal quantity of the colon bacillus, and that those immunized against from ten to twelve times the fatal dose of the colon germ succumb to three times the fatal quantity of the typhoid bacillus.

A second method of studying this question is founded on the discovery of Pfeiffer, that the blood serum of the animal immunized against the typhoid or cholera bacillus protects other animals against the germ used in securing immunity and not against others, *i.e.*, that the immunity is specific. The typhoid bacillus has been compared with the colon germ by the application of this test. Experiments of this kind have been made by Pfeiffer, Loeffler and Abel, Dunbar, Funk, and others. All have reached similar results. The blood serum of animals rendered immune to one of these germs does not give equal immunity against the other. In other words, judged by this test, the typhoid bacillus cannot be regarded as a variety of the colon germ. Furthermore, the application of the now well-known Widal test indicates the specific nature of the typhoid bacillus. However, these facts do not prove that the colon bacillus and the typhoid-like germs in drinking water are harmless, or that they may not induce fever. No less an authority than Gaffky has reported a case closely resembling typhoid fever in every detail, caused by the colon bacillus. That vaccination against smallpox does not protect against measles is no proof that the virus of the latter is harmless. Moreover, there are reasons for believing that too much reliance has been placed upon the Widal test, and that normal blood serum will

often have a similar effect upon the typhoid bacillus, and that the difference in behavior between the typhoid and colon germs towards the blood serum of typhoid patients is not so marked as has been generally believed.

Tuberculosis.

Koch's tuberculin is now regarded as the specific chemical poison of the bacillus tuberculosis. Koch prepared tuberculin in the following manner: Meat infusion containing one per cent. of peptone and from four to six per cent. of glycerin is placed in sterilized flasks with broad bottoms. The flasks are only partially filled in order that the surface of the fluid shall be as great as possible. A small mass of a growth of tubercle bacilli is taken from a culture on glycerin-agar or blood serum, and planted on the surface of the meat infusion in the flask. The flask is then placed in an incubator at 37° C. The bacilli grow abundantly on the surface of the meat infusion, forming a thick yellowish-white layer. After about six weeks growth stops; the bacterial layer also begins to break into pieces, and these fall to the bottom of the flask. The culture is now evaporated to one-tenth of its volume on the water-bath. The concentration increases the percentage of glycerin to from forty to fifty, and this ingredient prevents the growth of extraneous bacteria, and renders the fluid permanent for an indefinite time. After filtration through porcelain, this fluid constitutes the crude tuberculin of Koch. It is evident that it must contain in addition to the water and glycerin any other unchanged constituent of the original meat infusion, any split products, if there be such, arising from the cleavage action of the bacilli on the proteid constituents of the culture medium, and the soluble constituents of the bacterial cell. It is quite evident that the toxin, in the impure form, is not destroyed by the temperature of the water-bath. Ultimate analyses of this crude tuberculin have been made, but it must be evident from the statement just given concerning the complexity of its composition that such determinations are without value. It does not contain any ptomaïn or any cyanogen bodies. A voluminous precipitate occurs on the addition of strong alcohol, which precipitate contains the toxin. Since the toxin has not been isolated, its physical properties and chemical reactions remain for the most part unknown. The toxic substance is soluble and dialyzable. Bujwid prepared tuberculin by extracting growths of the tubercle bacillus on glycerin-agar tubes, heating to 100° C. for ten minutes, filtering through porcelain, and concentrating at a low temperature. The toxin may also be obtained from tubercle bacilli grown on potatoes. The freshly cut surfaces of the sterilized potatoes are

washed with a one-per-cent. sterilized solution of sodium carbonate, then washed with sterilized water containing five to six per cent. of glycerin. At a temperature of 37° C. the tubercle bacillus grows quite abundantly on potatoes thus prepared. After further development has ceased the growths are extracted with water and glycerin. Numerous attempts have been made to purify tuberculin, but up to the present time success has been at best only partial. Koch obtained a white precipitate containing the toxin by the addition of sixty per cent. of alcohol to crude tuberculin, but this precipitate is a mixture of several bodies. Hunter believed that he had separated the curative from the fever-producing constituent, but the former, as he obtained it, possesses no curative properties, and the latter is still a crude toxin. By fractional precipitation with alcohol Klebs has obtained a substance which he calls tuberculocidin.

Recently (1897) Koch has made a second most valuable contribution to our knowledge concerning the chemistry of the cell of the bacillus tuberculosis. The following is an abstract of the additional information which he has given us upon this point:

In the first place, he extracted tubercle bacilli with one-tenth normal soda solution. In doing this the bacilli were stirred up in the solution and allowed to stand at the room temperature with frequent agitation for three days. At the expiration of this time the fluid was filtered through paper and neutralized. In this manner there was obtained a faintly yellow fluid which was found never to be wholly free from bacilli. It contained in the ordinary cover preparation from five to ten bacilli in each field. These bacilli were never found in clusters but always single. Of course, the germs after this treatment are dead. This preparation, because it is an alkaline extract, is designed by Koch as TA. Experiments made with TA show that with very small doses a reaction similar to that caused by the original tuberculin follows. The only difference is that with TA the reaction is more marked and of longer continuance. With relatively large doses abscesses may form about the point of injection. These abscesses are filled with sterile fluid and may contain the dead bacilli. In order to remove the bacilli TA was filtered through porcelain. However, it was found that not only the bacilli but also a considerable amount of colloid substance remained on the filter. The filtrate was found not to produce abcesses, and not to exceed the reaction of the original tuberculin.

Koch regards the formation of the abscess by the injection of TA as an important fact, and holds that it teaches us that immunity against this disease cannot be secured by the subcutaneous injection of any fluid containing tubercle bacilli. Of course the amount of

this substance might be so small that abscesses will not follow. This is accounted for by the fact that the subcutaneous tissue is able to dispose of very few dead bacilli without injury to itself.

Former researches have convinced Koch that the tubercle bacilli contain at least two characteristic chemical bodies which belong to the unsaturated fatty acids. One of these fatty acids is soluble in dilute alcohol and is easily saponified with sodium hydrate. The other is soluble only in boiling absolute alcohol or ether, and is saponified with difficulty. Both of these take the characteristic stain of the tubercle bacilli, that is, they are colored an intense red with carbolic fuchsin, and retain this color after treatment with dilute nitric acid and with alcohol. Tubercle bacilli from which the first of these fatty acids has been removed by cold alcohol, still respond to the stain test for the germ. After the removal of both of these fatty acids from the bacilli, the cell still maintains its form, but no longer gives the specific coloration.

Finally, Koch has adopted the following method of preparing extracts of the tubercle bacilli: A well-dried culture is placed in an agate mortar and rubbed with an agate pestle until only a few of the bacilli respond to the specific stain. The powder thus obtained is suspended in dilute water and placed in a centrifugal machine. After this has revolved at the rate of four thousand revolutions per minute for one-half to three-fourths of an hour, it separates into a supernatant, opalescent fluid which contains no bacilli, and a sediment. The sediment is removed, dried, again rubbed in a mortar, and again placed in the centrifugal machine. There is now obtained a clear supernatant fluid and a solid sediment. These manipulations can be repeated as long as any extract is obtained from the bacilli.

The extracts thus obtained from the tubercle bacilli have been injected into men and animals, and it has been found that they do not produce abscesses. It has been found, however, that the extract first obtained differs from the second and subsequent extracts. The extract first obtained in the centrifugal machine is designated by Koch as TO, and the subsequent extracts as TR. The addition of fifty per cent. of glycerin to TO causes no change, while in TR it produces a white flocculent precipitate. This indicates that TR contains substances, extracted from the tubercle bacilli, which are insoluble in glycerin, while TO contains those substances which are soluble in glycerin. Corresponding to this chemical difference, these preparations act somewhat differently upon men and animals. TO resembles the original tuberculin and the preparation which has been already designated as TA, with the exception that TO does not cause abscesses. Moreover, TO has but little effect on the production of

immunity. On the other hand, TR acts differently so far as the production of immunity is concerned. It is true that when given in large doses it gives the tuberculin reaction, but its most important effect is entirely independent of this reaction. While in the use of the original tuberculin and of the preparations here known as TA and TO, the so-called tuberculin reaction must be induced in order to get any curative effect, Koch attempts in his employment of the TR preparation to avoid the tuberculin reaction. By beginning with small doses of the TR extract and gradually increasing the same, Koch claims that animals can be made immune to the TR preparation, and finally to the tubercle bacillus itself.

Koch states that not every culture of the tubercle bacillus is suitable for the preparation of the active TR extract. He has convinced himself that the tubercle bacillus is more variable in its virulence than has been heretofore supposed. Cultures kept for a long time in the laboratory and grown on artificial media lose their virulence in part. For the preparation of the TR extract the most virulent cultures should be employed, the less virulent ones furnishing a less active or wholly inert preparation. The cultures must not be too old, in fact, they must be used in as early a stage of their development as is possible. The bacilli must be dried in vacuo. Otherwise, the substance becomes less soluble and furnishes a less active preparation. The essential constituent of TR is shown to be highly susceptible to chemical and physical influences. The preparation must be carefully excluded from light.

Koch cautions against attempts to prepare these extracts on a small scale, and claims that they should be manufactured only in laboratories specially fitted for the purpose. Certainly the process of rubbing up highly virulent tubercle bacilli to a dry powder in a mortar is not to be regarded as altogether free from danger. Koch states that in doing this himself he did not use a respirator, but that he regards the preparation as scarcely less dangerous than that of working with highly explosive material. The TR extract is preserved by the addition of twenty per cent. of glycerin; which is not enough to cause the precipitation of its active constituents.

The practical application of this preparation is similar to that of the original tuberculin. Injections are made under the skin of the back with sterilized syringes. The fluid contains in each cubic centimetre 10 mgm. of solid substance, and when used it is diluted with physiological salt solution to the extent desired. The beginning dose is 0.05 mgm. Only in exceptional cases is the use of this amount followed by reaction. If a reaction should occur a smaller dose is employed. Koch repeats the injection every second day,

gradually increasing the dose, avoiding elevation of temperature. When there is an elevation of temperature following an injection subsequent treatment must be delayed until the normal temperature has been regained. Koch states that as a rule he has increased the dose of TR preparation until he has reached 20 mgm. In immunizing animals from 2 to 3 mgm. is used as a beginning dose in guinea-pigs; correspondingly larger amounts for other animals. In animals already tuberculous the beginning dose must be smaller.

Koch states that by proceeding in this manner he has succeeded in rendering a large number of guinea-pigs wholly immune against inoculations with the most highly virulent cultures of the bacillus. In some of these animals there was no reaction at the point of injection and the inguinal glands remained wholly unchanged for months. In others these glands were slightly enlarged, but were found not to be tuberculous. Some animals at the time of inoculation proved not to be immune. In these the inguinal glands underwent caseation. The internal organs, however, were free from tuberculosis, while control animals showed widely diffused general tuberculosis of the lungs, spleen, and liver. In other animals still less immune, inoculations were followed by tuberculosis of the lungs, while the liver and spleen showed only traces of the disease.

Tuberculous guinea-pigs treated with injections of the TR extract showed without exception more or less marked regressive changes in the tuberculous areas. For instance, in the liver instead of necrotic areas, one would observe depressions on the surface which were so numerous in many instances as to make the surface of the organ very uneven. In the spleen contractures were observed, and in some instances these involved so large a proportion of the organ that the part remaining was very small compared with the normal size of this organ. Koch states that he has been able to immunize guinea-pigs within from one to three weeks. For the cure of tuberculous guinea-pigs, the treatment must be begun soon after the inoculation; not later than two weeks. He also holds that this substance will be of value in the treatment of the early stages of tuberculosis in man.

This preparation has been already used by Koch in a large number of cases, including lupus as well as pulmonary tuberculosis. He states that these cases have been markedly improved by the treatment.

Whether or not Koch has succeeded at last in securing a curative agent for tuberculosis, it must be admitted that his work is of the highest scientific value and that he has furnished us with the most exhaustive research yet made on the chemistry of the tubercle bacillus.

Crookshank and Herroun some years ago reported the isolation of a ptomaïn and an albumin not only from artificial cultures of the bacillus tuberculosis, but also from the tissues of tuberculous cows. They state that the ptomaïn thus obtained causes an elevation of temperature in tuberculous animals, and a depression in healthy ones. "The albumin, whether obtained from the pure cultivations of the bacilli or from tuberculous tissue, produced a marked rise of temperature in tuberculous guinea-pigs. On the other hand, in an experiment tried on a healthy guinea-pig there was an equally well-marked fall of temperature."

Zuelzer reported the isolation of a poisonus base from the cells of the bacillus tuberculosis taken from agar cultures. He states that 1 cgm. or less of this substance injected subcutaneously in rabbits or guinea-pigs causes after from three to five minutes increased frequency of respiration, and an elevation of temperature from 0.5° to 1° C. He also reports marked protrusio bulbi as a constant symptom of the action of this substance. He states that the eyes become very bright and that the pupils are dilated. A dose of from 2 to 3 cgm. kills rabbits, death occurring in from two to four days after the injection. The tissue about the place of injection is reddened, and hemorrhagic spots are found in the mucous membrane of the stomach and small intestine. In two instances, from 15 to 20 c.c. of clear fluid were found in the peritoneal cavity.

Even before Koch announced the discovery of tuberculin, Hammerschlag had reported the presence of a toxin among the products of the growth of this germ. More recently he has interested himself in an analysis of the cellular substance of the bacillus tuberculosis. He finds that twenty-one per cent. of this substance is soluble in alcohol and in ether. In these extracts there is, in addition to fat and lecithin, a poison which induces convulsions followed by death, in guinea-pigs and rabbits. The part insoluble in alcohol and ether consists of proteids and cellulose. The same investigator has prepared from cultures of this bacillus a toxalbumin which, when injected subcutaneously in rabbits, causes an elevation of temperature of from 0.1° to 0.2° C.

The physiological action of tuberculin is so pronounced, and at first was believed to be so markedly *sui generis*, that it astonished the medical world and led to the ready acceptance of the belief that at last a positive cure for tuberculosis had been discovered. The most characteristic effects of tuberculin are as follows:

1. Small doses, 1 mgm. or even less, injected subcutaneously in an individual suffering from tuberculosis cause a marked elevation of temperature. Similar doses injected in the same way into non-

tuberculous persons produce no appreciable effect, and persons sick with other diseases than tuberculosis are unaffected by small doses. Here then is a body that has a specific action, a chemical substance by the effects of which one can distinguish a tuberculous from a non-tuberculous individual. If all cows of a large herd, for instance, be treated with tuberculin and the record of the temperature be made for twenty-four hours before and for the same time after the treatment, it will be found that in some a febrile reaction—an elevation of 1° or more in temperature—occurs, while the temperature of the others remains unaffected. If all these animals be killed and examined it will be found that those which manifested the febrile reaction are tuberculous, while those which failed to react are non-tuberculous. Koch first made this experiment upon tuberculous and non-tuberculous guinea-pigs. No such effect had ever before been obtained by the employment of any therapeutic agent. It is small wonder then that Koch and his co-laborers were surprised with the results observed, and readily accepted the belief that a specific cure for tuberculosis had been found. The grounds for this belief were strengthened by their observation of the additional evidence of the selective action of tuberculin.

2. Not only does tuberculin select tuberculous individuals by its action, but in the individual it selects, for the demonstration of its most conspicuous effects, the exact site of the tuberculous lesion. If a man who has a lupus on his face receive a tuberculin injection in the back or in any other portion of his anatomy, the tissue about the lupus soon shows evidence of stimulation. It becomes hyperæmic, the margins of the sore begin to granulate, and if the treatment be continued the lupus often temporarily heals. It is now known that a number of other substances, among which we may specially mention the albumoses, have a similar selective action for tuberculous areas. Baumgarten sums up his experiments with tuberculin on rabbits as follows: It causes an exudative inflammation in the vascular tissue about the tubercles. In this way the tuberculous tissue may be isolated and, when located superficially, removed. In some cases, however, after the prolonged employment of the agent the tuberculous tissue itself may, under the influence of the exudative fluid and the polynuclear leucocytes, break down and form abscesses.

The tubercle bacilli are in no way hurt by the use of tuberculin, and after its constant employment for months in tuberculous animals the bacilli retain their original form and lose none of their virulence. Some experiments seem to show that the bacilli multiply more rapidly when the injections are made, but a positive statement on this point is reserved. It is certain, however, that the non-tubercu-

lous tissue of the animal acquires no immunity against the disease. This is shown by the appearance of metastatic foci in animals in which from 7 to 12 gm. of crude tuberculin have been injected. It is further shown by the fact that in some animals treated subcutaneously tubercles have appeared at the point of injection.

Prudden and Hodenpyl reached some interesting results in their experiments, which consisted of the inoculation of animals with dead tubercle bacilli. These authors make the following statement: "These dead tubercle bacilli are markedly chemotactic. When introduced in considerable amount into the subcutaneous tissue or into the pleural or abdominal cavities they are distinctly pyogenic, causing aseptic localized suppuration. Under these conditions they are capable, moreover, of stimulating the tissues about the suppurative foci to the development of a new tissue closely resembling the diffused tuberculous tissues induced by the living germ. We have found that dead tubercle bacilli introduced in small numbers into the blood-vessels of the rabbit largely disappear within a few hours or days, but that scattering individuals and clusters may remain here and there in the lungs and liver, clinging to the vessel walls for many days without inducing any marked changes in the latter. After a time, however—earliest in the lung, later as a rule in the liver—a cell proliferation occurs in the vicinity of these dead germs which leads to the formation of new multiple nodular structures, bearing a striking morphological resemblance to miliary tubercles. There is in them, however, no tendency to cheesy degeneration and no evidence of proliferation of the bacilli, but rather a steady diminution in their number. It seems to us that the new structures originate in a proliferation of the vascular endothelium under the stimulus of the dead and disintegrating germs."

It has been shown by Maffucci and others that when animals are treated repeatedly with cultures of the tubercle bacillus sterilized by repeated heating from 65° to 70° C. there results a progressive marasmus which terminates fatally within from fourteen days to five or six months. Maffucci also finds that eggs inoculated with sterilized cultures of the chicken tuberculosis bacillus produce chicks which are feeble and soon die of emaciation.

Suppuration.

In 1888 Leber reported that he had extracted with alcohol from dried cultures of the staphylococcus a substance which proved to be markedly pyogenic. From this extract he subsequently obtained a crystalline body to which he gave the name phlogosin. This sub-

stance is readily soluble in alcohol and ether, sparingly soluble in water, and it crystallizes in needles. With moderate heat it can be sublimated, leaving no residue, and the sublimate which forms in rosettes still possesses pyogenic properties. From its solutions this substance is precipitated by alkalies in amorphous granules which dissolve in acids, forming crystalline salts.

Christmas filtered bouillon cultures of the pyogenic cocci and precipitated in the filtrate with alcohol an albuminous substance which when administered to animals induced effects similar to those caused by phlogosin. Hoffa obtained the poisonous substance known as methyl guanidin from the bodies of rabbits dead of septicæmia. Brieger and Fraenkel supersaturated filtered cultures of the staphylococcus with ammonium sulphate, removed the salt by dialysis, and evaporated the solution of the toxin at 40° C. in vacuo. The concentrated solution thus obtained killed animals when administered subcutaneously within twenty-four hours. Rodet and Courmont found that the previous treatment of animals with the chemical products of the staphylococcus rendered them more susceptible to inoculation with the germ. They furthermore observed that the kidney lesions were much more marked when the inoculations were preceded by injections of the chemical poison. By treating filtered cultures with alcohol they obtained an insoluble body with which they immunized animals to the germ, while a substance soluble in alcohol increased the susceptibility of the animals. Donath induced fever in animals by intravenous injections of from 10 to 20 c.c. of cultures sterilized at 63° C. Fermi believes that the pathogenic properties of the staphylococcus are due to the acids produced by it, the most prominent of which are propionic, butyric, lactic, and valerianic.

Wolf has made a series of experiments more interesting in the suggestions to which they give rise than in the results obtained. He placed collodion sacks filled with cultures of the staphylococcus in the abdominal cavities of rabbits, having previously ascertained that the soluble products would diffuse through the collodion while the germs would be retained. The results were somewhat contradictory even when the sacks were not broken, and when their contents were found to be sterile, as sometimes happened, staphylococci were found in the peritoneal cavity. Wolf suggests that these may have come from the intestines. This suggestion is strengthened by the fact that colon germs were also found in the peritoneal cavity. This theory supposes that the chemical poison so alters the physiological activity of the intestinal walls that bacteria pass from the lumen of the intestine into the peritoneal cavity.

Marmorek has so intensified the staphylococcus by carrying it

through a series of animals that the one hundred millionth of a cubic centimetre of a culture injected subcutaneously in rabbits caused death within thirty hours. He has also rendered animals immune to this germ and has obtained an active antitoxin. This antitoxin has been used to some extent in the treatment of septicæmias, but the evidence concerning its value is at present too limited and too contradictory to enable us to reach any positive conclusion concerning its value.

The possibility of converting toxins into antitoxins by means of electricity has been a matter of experimentation. Smirnow was the first, I believe, to try to cause this conversion. He used the diphtheria toxin and was partially successful. He explained the conversion as due to changes in reaction in the fluid. D'Arsonval and Charrin and Bolton have experimented along this line, also with partial success. Bonome and Viola conclude their experiments on streptococcus toxin with the following conclusions:

1. A high alternating current renders the most virulent cultures of the streptococcus harmless without changing the reaction of the culture or affecting the form of the germ.

2. This action of the current is confined to the toxin. The germ when transferred to other tubes grows and manifests its full virulence.

3. The toxin is transformed into antitoxin analogous to that of the blood serum of immunized animals.

4. The antitoxin thus formed is very active, and will neutralize *in vitro* ten times the usual fatal dose of a culture. However, from a recent culture only a small amount of antitoxin can be obtained because such cultures contain but little toxin.

5. This antitoxin possesses powerful protective and curative action against streptococcus infection.

6. While this antitoxin is a true vaccine like that obtained by heating cultures to 55° to 60°, it is not without injurious effect, and induces in rabbits a progressive marasmus preceded by an elevation of temperature.

7. This antitoxin has the property of developing in rabbits substances which destroy the germ. *In vitro* it leads to degenerative changes in the germ cells. These changes, however, proceed slowly.

The presence of pyogenic substances in the cells of many varieties of bacteria has been demonstrated by Buchner. The amount of these substances varies with the kind of germ, and some species seem to contain no such bodies. The bacillus pyocyaneus contains a large quantity of a pyogenic proteid. This can be prepared as follows: The germs are taken from potato cultures and rubbed up with water. Then they are treated with about fifty volumes of a 0.5-per-cent. solu-

tion of caustic potash. In the cold this forms a mucilaginous mass which dissolves at the temperature of the water-bath. After being heated for some hours the fluid is filtered through a number of filters; the first portions should be refiltered. The filtrate is a greenish fluid and by the careful addition of acetic or hydrochloric acid to this a voluminous precipitate is obtained. This precipitate should be collected on a filter, washed with water, then suspended in water, and a few drops of the soda solution added, when a dark-brown fluid with a tendency to gelatinize in the cold, containing about ten per cent. of the proteid, is obtained.

Buchner tested the action of this proteid upon himself. One cubic centimetre of a very dilute solution containing 3.5 mgm. of the solid proteid was injected under the skin of the forearm with antiseptic precautions. Two hours later there was marked pain along the lymphatics, especially localized about the elbow and axilla. The temperature at this time showed no marked elevation. On the following day there was a marked erysipelatous redness with some swelling extending for some inches about the place of injection, and accompanied by severe pain. The inflamed area felt hot and projected distinctly above the surrounding surface. The lymphatics of the arm appeared like red cords. On the third day the swelling and redness were more marked and extended from the wrist to the elbow. On the fourth day the symptoms began to recede. Buchner claims that all the cardinal symptoms of inflammation—rubor, calor, dolor, tumor—were present and that these could not be produced without involvement of the solid tissues.

Nannotti treated animals with sterilized pus and reached the following conclusions:

1. Sterilized pus has subtantially the same toxic properties as have sterilized cultures of the staphylococcus.

2. Repeated injections of sterilized pus induce chronic intoxication and marasmus.

3. Injections under the skin cause a specially grave form of poisoning.

4. The symptoms and pathological lesions caused by these injections correspond with those observed in men suffering from chronic suppuration.

Hog Cholera.

In pure cultures of this bacillus Novy found a poisonous base which probably has the composition $C_{10}H_{26}N_2$, and to which he has provisionally given the name susotoxin. One hundred milligrams of the hydrochloride of this base produced in white rats convulsive

tremors and death within one and one-half hours. Section shows the heart in diastole, the lungs pale, the stomach contracted, a serous effusion in the thoracic cavity, and the subcutaneous tissue pale and œdematous. Novy has also obtained a poisonous proteid or toxin from cultures of this bacillus. The following experiments illustrate the effects obtained by this body: 100, 50, and 25 mgm. respectively were injected into three young rats from the same litter. The one receiving 100 mgm. soon began to crawl about on its belly, being unable to rise. The eyes were filled with a thick secretion and the toes became red. Finally it became quiet, lying on its belly with feet extended. The respirations became deeper and a coma-like condition set in. The animal died without convulsions within about three hours. The animal that received 50 mgm. presented the same symptoms and death resulted in four hours. The one which received 25 mgm. became very sick, but finally recovered, and a week later it was given another injection of 30 mgm., which produced scarcely any effect. Then it was treated at intervals of five, three, five, two, and four days respectively with 40, 50, 75, 100, and 125 mgm. without effect. Three days after the last injection the animal was inoculated with 1 c.c. of the bouillon culture of the highly virulent germ. Only a slight temporary effect was observed during the first day, after which recovery was complete and permanent. A control rat to which was given the same quantity of the culture sickened the next day and died one week later.

From cultures of the same bacillus de Schweinitz has reported the separation of a slightly poisonous base and a poisonous proteid. The proteid body is classed by this author among the albumoses, and is said to crystallize in white translucent plates when dried in vacuo over sulphuric acid, and to form needle-like crystals with platinum chloride. This is interesting in view of the fact that no one else has reported a crystalline bacterial proteid. The same author reports the isolation of a soluble ferment from cultures of the hog-cholera germ, and states that injections of these soluble ferments confer immunity.

Glanders.

The toxin of this disease is contained in the bacterial cell and is known as malleïn or morvin. Sterilized cultures of the glanders bacillus containing the toxin are now used for the purpose of diagnosing the disease in horses in the same way that tuberculin is employed to detect tuberculosis in cows. The subcutaneous injection of small quantities of malleïn causes a more marked elevation of temperature in glandered horses than it does in healthy ones. It has

been shown by the researches of Schattenfroh that there is nothing specific in this action of malleïn, inasmuch as the same effect is produced in glandered horses by the injection of toxins obtained from other bacteria. There are numerous methods of preparing commercial malleïn; one of these is as follows: Growths of the glanders bacillus from ten to fourteen days old on potatoes are removed with a sterilized spatula, and rubbed up with sterilized water in the proportion of one part of the moist bacilli to nine parts of water. This emulsion is allowed to stand for twenty-four hours, then heated to 110° C. for five minutes; next it is filtered through porcelain, thirty per cent. of glycerin is added, and it is concentrated at a low temperature on the water-bath to one-eighth of its original volume. This is again sterilized at 110° C. The preparation is now ready for use, and consists of a clear, yellowish, odorless fluid of feebly acid or neutral reaction. It is unnecessary to state that this preparation contains numerous substances. Kressling found in it peptones, globulins, xanthin, guanin, small quantities of tyrosin and leucin, and traces of volatile fatty acids and ammonia.

Rabbit Septicæmia.

Hoffa has isolated from the bodies of rabbits dead from this disease methyl guanidin, while in the bodies of healthy rabbits this poison could not be found. The fatal dose of methyl guanidin for rabbits is about 0.2 gm when given subcutaneously. There is some reason for believing that methyl guanidin is produced by the bacillus of chicken cholera also; in fact, as Hueppe has suggested, the bacterium of chicken cholera is probably identical with that of rabbit septicæmia.

Malignant Œdema.

Kerry has found in cultures of the bacillus of this disease a foul-smelling, oily substance of the composition $C_8H_{16}O_4$. This oil is insoluble in water, alkalies, and acids; easily soluble in ether, benzol, bisulphide of carbon, and alcohol. No experiments have been made with it upon animals and consequently there is no proof that it is poisonous.

LEUCOMAÏNS.

A leucomaïn may be defined as a basic substance originating in the metabolic processes taking place in the animal body. Leucomaïns closely resemble the vegetable alkaloids, and many of them are found in plants as well as in animals. For instance, vegetable tissues

are known to contain such bases as xanthin, hypoxanthin, and certain other substances closely related to these, as caffeine and theobromine. In both plants and animals these basic substances originate in similar bodies, as nuclein and lecithin. It is quite impossible to draw a sharp line of distinction between those substances which result from the activity of the cells of various organs of the body, and those which may be formed by bacterial agency in the intestines and then be absorbed into the blood and eliminated in the urine. In fact, some physiological chemists have suggested that many of these basic bodies are bacterial products formed in the intestine, absorbed, and eliminated, as suggested above. That there are ptomaïns which originate in this way can no longer be doubted. The researches of Baumann and Udransky have demonstrated that the cadaverin and putrescin which occur in the urine in cystinuria are formed by bacterial processes in the intestinal tract. The same is true of alkapton, which probably is formed by the action of bacteria on tyrosin. Undoubtedly phenol, skatol, and indol originate in the intestines and are due to bacterial fermentation. However, an endeavor will be made in this paper to confine the discussion to the true leucomaïns which, as has been stated, originate in the metabolism of the animal cell itself.

The leucomaïns are naturally divided into two distinct and well-defined groups. These are (1) the uric-acid group, and (2) the kreatinin group. We will now proceed to a discussion of the more important members of the first of these groups.

Leucomaïns of the Uric-Acid Group.

Adenin, $C_5H_5N_5$.—This is the least complex of the uric-acid group of leucomaïns. As is seen from its formula, it is a polymer of hydrocyanic acid. This view of its chemical constitution is confirmed by the fact that on being heated with potassium hydrate to 200° C. it yields potassium cyanide. Under the influence of reducing agents it is converted into a substance similar to, possibly identical with, azulmic acid. Adenin has not been prepared synthetically, although Gautier has claimed to have synthesized two closely allied bodies, xanthin and methyl xanthin, by heating hydrocyanic acid in sealed tubes in contact with water and acetic acid. Adenin was discovered by Kossel in 1885. It was first prepared from pancreatic glands. It has been shown to occur together with guanin, hypoxanthin, and other members of this group as a decomposition product of nuclein, and it may be obtained from all tissues, animal or vegetable, which are rich in nucleinic acid. The thymus gland is especially rich in

this base and furnishes probably the best source for its preparation. In fact, the nucleinic acid from this gland yields only adenin and no xanthin. Adenin has been obtained from the urine of leucocythæmic patients, and also from the liver of such a patient after death. Since this disease is characterized by the presence of an unusually large number of nucleated white blood corpuscles it is easily seen that these constitute a source for this base. It does not occur at all or is present only in minute traces in meat extracts. This is explained by the fact that muscular tissue is very poor in nucleated cells, and consequently contains a very small amount of nuclein. In fact, it is altogether probable that the greater part of the xanthin bases found in muscle tissues do not originate in muscle cells, but owe their presence in this tissue to blood and lymph.

There can be but little doubt that adenin is intimately concerned in the physiological function of the cell nucleus. In the nucleus adenin does not exist in the free state, and probably results only as a decomposition product of the nuclein. Nuclein, which must be regarded as the parent substance of adenin and guanin, is the best known and evidently the most important constituent of the nucleus, and as such it has been credited with a direct relation to the reproductive powers of the cell. It is generally regarded as an established fact that non-nucleated cells are incapable of reproduction. Lillienfeld has made the most exhaustive study of the chemistry of the leucocytes, and in this he has shown that these contain a complex body to which he has given the name nucleohiston. This substance may be decomposed by acids into histon and leuconuclein. The latter, upon being further treated with mineral acids, yields albumin and nucleinic acid, and the nucleinic acid can be broken up into phosphoric acid, nuclein bases, and unknown substances. Nucleinic acids from different sources differ in the kind and amount of nuclein bases which they may yield. For instance, the nucleinic acid obtained from the thymus gland yields only adenin, and for this reason it is sometimes called adenylic acid. Some vegetable substances yield considerable amounts of adenin; for instance, extract of tea leaves may yield from 3 to 6 gm. of this base per litre. When obtained from impure solutions adenin appears either as an amorphous substance in pearly plates, or in very small microscopic needles. From pure solutions it separates in needle-shaped crystals which contain three molecules of water. The water of crystallization is given off on exposure to the air or on heating to 53° C. When this water is driven off the crystals become opaque. On the addition of ammonia to an aqueous solution of the hydrochloride of adenin the base is precipitated in an anhydrous

form, appearing as small whetstone-shaped crystals, and these when recrystallized from hot water form four-sided prisms. Adenin is very sparingly soluble in cold water, more readily soluble in hot water, crystallizing from the latter on cooling. Its aqueous solution is neutral in reaction. The free base is insoluble in alcohol, chloroform, and ether, soluble in glacial acetic acid, and slightly soluble in hot alcohol. When treated with dilute mineral acids it dissolves readily, forming easily crystallizable salts. It is readily soluble in the fixed alkalies, but on neutralization of these solutions it is reprecipitated, appearing in large anhydrous crystals. Adenin can be heated to 278° C. without melting, but at this temperature it becomes slightly yellow and yields a white sublimate. Pure adenin does not give the so-called xanthin reaction. That is to say, when a solution of adenin is evaporated on the water-bath with nitric acid it gives a white residue which fails to give any coloration on the subsequent addition of ammonia. It also fails to give Weidel's reaction—*i.e.*, on being heated with fresh chlorine water and a trace of nitric acid as long as gas is given off, then evaporating on the water-bath and exposure of the residue to an ammoniacal atmosphere, it does not give the coloration characteristic of this reaction. On the addition of ferric chloride to an aqueous solution of adenin an intense red color not affected by heating is produced. Copper sulphate forms with solutions of adenin an amorphous grayish-blue precipitate which is easily soluble in dilute acids and ammonia. The readiness with which adenin may be transformed into other xanthin bases is shown by the fact that in its extraction from tea leaves, after the removal of caffeine, if urea be not added to the nitric acid used, nearly one-half of the adenin may be converted into hypoxanthin. Many bacteria are capable of converting adenin into hypoxanthin. A similar change takes place rapidly in the pancreas after death. In fact, adenin undergoes decomposition of this kind much more rapidly than other xanthin bases. Adenin and guanin are regarded as the antecedents not only of hypoxanthin and xanthin, but also of intermediate products, which when formed in the cell may give rise to important chemical processes, especially those of a synthetic nature.

Numerous compounds of adenin have been produced artificially and thoroughly studied, but descriptions of these would hardly be in place in this paper. But little is known concerning the physiological action of this base. When given in very large doses it is poisonous, and is eliminated at least in part in the urine unchanged.

Hypoxanthin, $C_5H_4N_4O$.—This base, once known as sarkin, was discovered by Scherer in 1850 in the pulp of the spleen, and also found in the muscles of the heart. The name hypoxanthin was

given to it because it contains one atom of oxygen less than xanthin. Like adenin, it may be obtained from nearly all of the animal tissues which are rich in nucleated cells. It has been found in the blood after death, but not in that drawn from the blood-vessels during life, except in pathological conditions. However, failure to find it in the blood of the living animal is probably due to its presence in this fluid in very minute quantity, because it is known to be a normal constituent of the urine. In the blood and in the urine of leucocythæmic patients it is present in abnormally large amount. Very rarely hypoxanthin forms a deposit in the urine, and in these cases it is easily confounded with uric acid on account of its crystalline shape. Thudichum has obtained it from the urine of persons sick with various structural diseases of the liver and kidney. It has been found along with uric acid in various exudates and transudates. It has also been obtained from the brain, from muscle, from the marrow of bones, from the kidney, heart, spleen, and liver. It is found in considerable quantity in the spawn of salmon, in the testicles of the bull, in the nuclein of pus, and traces of it in red blood corpuscles. It has also been found in the pollen of various plants, in the seed of black pepper, in oats, wheat, potatoes, and in yeast. Demant has shown it to be relatively abundant in the muscles of pigeons in a state of inanition, while in the muscles of well-fed pigeons it is said to be wanting. Salomon found both hypoxanthin and xanthin in the cotyledons of lupine and in the sprouts of malt. It occurs along with adenin, xanthin, and theophyllin in tea leaves. It is possible that its presence in some of these substances may result from the oxidation of adenin. It will be seen from the above that this is a widely distributed base, in fact it may be found in any cells containing nuclein, either as preëxisting in such cells or as formed from the oxidation of adenin. It has been shown that fresh eggs yield a smaller quantity of this base and of other xanthin bases than do those eggs in which the embryo has begun to develop. This is due to a very important fact observed by Kossel, that the nuclein of undeveloped eggs differs from the nuclein of cell nuclei. While the nuclein from cell nuclei decomposes into xanthin bases, that from undeveloped eggs yields no nitrogen bases on treatment with acids. As the egg develops the nucleated cells increase in number, and consequently the embryo chick yields the xanthin bases. The hypoxanthin which is found in muscle appears to exist in a preformed state, and can be extracted from this tissue by water. When a mixture of guanin, xanthin, and hypoxanthin is allowed to putrify these bases disappear in the order named. In other words, hypoxanthin resists bacterial action longer than guanin and xanthin. When adenin undergoes

putrefaction in the absence of air it is converted into hypoxanthin, and guanin under similar conditions is changed into xanthin. In these conversions an imido group is replaced by oxygen, and the imido group probably goes to form urea. This is an important fact, since the process of putrefaction is in certain respects analogous to some of the vital processes, and similar chemical changes may take place in animal organs. Hypoxanthin may be obtained from adenin by the action of nitrous acid. The relation of hypoxanthin to uric acid has been shown by Kruger, who demonstrated that the constitution of hypoxanthin is closely connected with that of uric acid. Fisher demonstrated the relation of uric acid to the xanthin bases by changing brom-theobromine into a uric-acid derivative. When administered to animals hypoxanthin is oxidized, first to xanthin, and then to uric acid.

Hypoxanthin is a white, colorless, generally amorphous, though sometimes crystalline, powder. It is soluble in about three hundred parts of cold water. It is more easily soluble in boiling water, and on cooling it crystallizes. Its solubility in cold alcohol is very slight. With acids and alkalies it easily passes into solution without decomposition, and from the latter solutions it can be precipitated by treatment with a current of carbonic-acid gas or by the addition of acetic acid. Its aqueous solutions are neutral in reaction. This base can be heated to 150° C. without decomposition, but above this temperature it sublimates and partially decomposes with the evolution of hydrocyanic acid. When heated with potassium hydrate to 200° it forms potassium cyanide and ammonia. When heated to the same temperature with water it decomposes into carbonic acid, formic acid, and ammonia. When evaporated with an oxidizing agent, such as chlorine water and nitric acid, the residue gives, on being brought in contact with the vapor of ammonia, a rose-red solution. However, Kossel claims that this is due to the presence of xanthin and that pure hypoxanthin does not give this test. With acids it forms crystalline compounds, and like the amido-acids it also forms compounds with bases and with certain metallic salts, such as silver nitrate and copper acetate.

In doses of 100 mgm. administered to frogs, it causes increased reflex excitability and convulsive seizures. It is slow in its action, requiring from six to twenty-four hours to produce the above-mentioned effects. One hundred milligrams may prove fatal to frogs. When injected subcutaneously into hepatotomized geese or when fed to chickens, it increases the amount of uric acid eliminated in the urine. This conversion is analogous to that observed by Stadthagen in the case of guanin, and further demonstrates that in the xanthin

bodies we have antecedents of uric acid apart from the synthesis of the latter from ammonia in the liver. The process by which this change is induced is undoubtedly one of oxidation.

Guanin, $C_5H_5N_5O$.—This base was discovered in 1844 by Unger in guano. It is an interesting fact that guano yields varying quantities of this substance, according to the region from which it comes. Thus, Peruvian guano contains the largest proportion, and on that account this variety is employed when it is desired to prepare guanin. Since its discovery, guanin has been found in a large number of tissues, both animal and vegetable. It has been found in the liver, pancreas, lungs, retina, in the thymus gland of the calf, and in the testicles of the bull; also in the scales of certain fish and in the excrement of birds and of insects. It has also been found in the spawn and testicles of the salmon, in the young leaves of vines, and in grass, clover, and oats, as well as in the pollen of various plants. It has been isolated from yeast which has been allowed to stand in contact with water for some time at the body temperature. Pathologically it occurs in the muscles, ligaments, and joints of hogs suffering from the disease known as guanin gout. Normally it is present in cell tissue only in traces. Its presence in the urine of man has never been satisfactorily demonstrated, although it has been reported, but it is possible that in these instances xanthin has been mistaken for guanin. It has been found in considerable amount in certain exudates and transudates. In some of the lower animals guanin is to be regarded as a normal product of metabolism, inasmuch as it is excreted in the urine. Our knowledge as to the origin of this and other allied bases is largely dependent upon the brilliant researches of Kossel and his pupils, who have shown that nuclein is an essential constituent of all nucleated cells, whether animal or vegetable, and that nuclein under the influence of water or dilute acid decomposes into adenin, guanin, hypoxanthin, and xanthin. We have also learned that the first two of the above-mentioned bases are readily converted by the action of nitrous acid into the other two, that is to say, an NH-group in these bases is replaced by an atom of oxygen—a change which it is not at all unlikely takes place in the tissues, perhaps in every cell nucleus. The probability of such a change is rendered more certain by the experiment of Schindler, who has shown that under the influence of putrefactive changes adenin and guanin are converted, respectively, into hypoxanthin and xanthin. If this explanation be correct, then adenin and guanin are to be regarded as transition products between the complex proteid molecule on the one hand and hypoxanthin and xanthin on the other. The last two in turn form the connecting link to the last step in the

retrograde metamorphosis of the nitrogenous elements of the cell. It is an interesting fact that a new base, to which the name vernin has been given, has been found in vetch and ergot. This base has the formula $C_{16}H_{20}N_8O_8$, and it is of special interest at this point since on being heated with hydrochloric acid it yields guanin. This indicates that we have two sources of guanin, the nucleins and vernin. Like adenin, guanin occurs in animal muscle only in traces, a fact which is explained on the ground that the muscle tissue is poor in nucleated cells. As the muscle cell has become morphologically differentiated from the typical cell, it may be looked upon as having undergone a chemical differentiation, inasmuch as we no longer find phosphoric acid, xanthin, and hypoxanthin in the same chemical combination as they occur in the original cell. In muscle, phosphoric acid exists, largely at least, in the form of a salt. Correspondingly, xanthin and hypoxanthin occur in its tissue in the free state and can be easily extracted with water.

Guanin may be prepared from Peruvian guano by repeatedly boiling this substance with milk of lime until the liquid becomes colorless. The residue, which consists largely of uric acid and guanin, is boiled with a solution of sodium carbonate, filtered, and the filtrate, after the addition of sodium acetate, is acidulated with hydrochloric acid. A precipitate is formed and contains guanin along with some uric acid. This precipitate is dissolved in boiling hydrochloric acid and the guanin thrown out of solution by the addition of ammonium hydrate.

Pure guanin forms a white, amorphous powder, insoluble in water, alcohol, ether, and dilute ammonium hydrate. It is readily soluble in mineral acids, in fixed alkalies, and in an excess of concentrated ammonium hydrate. It can be heated to 200° C. without decomposition. When a solution of guanin is evaporated with strong nitric acid it leaves a yellow residue which on the addition of sodium hydrate assumes a red color, and this on being heated becomes purple and then indigo blue. On cooling it returns to a yellow, passing through purple and reddish-yellow shades, due probably to the absorption of water. This constitutes the so-called xanthin reaction, and is supposed to be due to the formation of xanthin and a nitro product. This test is best given by guanin, less distinctly by xanthin, and is not given by hypoxanthin or adenin.

Guanin is a very feeble base, as is demonstrated by the fact that some of its salts readily dissociate on contact with water, especially at a high temperature. Physiologically, guanin is believed to be wholly inert.

Xanthin, $C_5H_4N_4O_2$.—This base was discovered by Marcet in 1819,

who found it as a constituent of a urinary calculus. Since that time it has frequently been found as the only or chief constituent of many calculi. Like the other bases of this group, it is widely distributed. It is a normal constituent of the urine, but is present only in minute quantities. It is stated that during the use of sulphur baths or after the thorough application of sulphur salves to the skin, the quantity of xanthin in the urine is considerably increased. It is present in unusually large quantity in the urine of leucocythæmic persons. It has also been found in the urine of persons suffering from pneumonia, and Baginsky claims that the amount of xanthin normally present in the urine may be increased tenfold in cases of acute nephritis. Many years ago Bence Jones observed in the urine of a child sick with renal colic a deposit of crystals which he considered to be xanthin, but other observers are inclined to regard these crystals as those of hypoxanthin. The writer once found a large amount of xanthin deposited in the urine of a patient with an enlarged spleen. Gautier claims to have succeeded in synthetizing not only xanthin, but also its homologue, by simply heating hydrocyanic acid in a sealed tube with water and a little acetic acid, the latter being added to neutralize any ammonia that might be produced.

Pure xanthin is a white, granular, amorphous substance. It is soluble with difficulty in cold water, alcohol, and ether, more readily soluble in boiling water. It is easily soluble in alkalies and alkaline carbonates, but not in the bicarbonates, and from these solutions it is precipitated on neutralization with acid, or on treatment with a current of carbonic acid. In warm ammonia it is more readily soluble than uric acid or guanin, and on cooling this solution it readily crystallizes. It is a weak base and also shows the properties of a weak acid. With salts of some of the heavy metals it forms feebly soluble or insoluble compounds. Its basic properties are much less marked than are those of hypoxanthin and guanin. Urinary calculi consisting of xanthin appear as brown fragments which on being rubbed with the finger assume a waxlike appearance. Xanthin, as obtained from the urine, has a yellowish tint due to the adherence of coloring matters. If a solution of xanthin be evaporated with nitric acid it leaves a lemon-yellow residue, which is not changed by exposure to vapor of ammonia; but with potassium hydrate it becomes yellowish red, and purple red on the application of heat. This reaction is not given by hypoxanthin or by adenin. When treated with a mixture of the hypochlorite of lime and sodium hydrate in a watch-glass, the solution becomes covered with a dark-green scum, which changes to brown and soon disappears. This test affords a means of distinction from hypoxanthin. It is an interesting fact that xanthin may be

converted into theobromine, the active constituent of theobroma cacao. Theobromine is dimethylxanthin, and this may be converted into trimethylxanthin, which is caffeine. Xanthin exists together with adenin, hypoxanthin, and caffeine, and possibly guanin, in tea leaves.

Little need be said concerning the physiological significance of xanthin. It bears the same relation to guanin that hypoxanthin does to adenin, and it is to be regarded as an intermediate compound, a step lower than guanin and nearer the limit of oxidation, as it occurs in the body, which limit is represented by uric acid. It is altogether probable that the xanthin formed in the body is oxidized into uric acid almost as rapidly as it is formed. In its physiological action it is a muscle stimulant, acting especially upon the heart. In frogs it produces decided muscular rigor, and in large doses paralysis of the cord. In its action it is probably stronger than either caffeine or theobromine.

Heteroxanthin, $C_6H_6N_4O_2$.—This base was first isolated from the urine by Salomon in 1884. Chemically it is methylxanthin and is intermediate between xanthin and paraxanthin or dimethylxanthin. Heteroxanthin and paraxanthin exist in about the same amount in the urine of man and that of the dog. It is believed by Salomon that this substance, as well as paraxanthin, is formed in the kidney. The reason for this belief is founded upon a failure of this observer to find either of these bases in the liver or muscles. It is stated that both paraxanthin and heteroxanthin are absent from the urine of the cow. Unlike the other xanthin bodies, heteroxanthin has not, as yet at least, been obtained from plants or from guano. The small amount of the xanthin bases in urine will be recognized from the statement that from 10,000 litres of urine Kruger and Salomon obtained 13 gm. of xanthin, 12.5 gm. of paraxanthin, and 7.5 gm. of heteroxanthin.

This base forms a white amorphous powder, which after prolonged contact with water may change into a crystalline body. It is sparingly soluble in cold water, much more easily soluble in hot water, and the solutions thus obtained are neutral in reaction. It is insoluble in alcohol and ether and readily soluble in ammonium hydrate. Like uric acid, it is freely soluble in piperazin. When heated, it readily volatilizes and gives off traces of hydrocyanic acid. On evaporation with nitric acid over the water-bath it leaves a white residue, which on the addition of sodium hydrate develops only a trace of reddish coloration.

As has already been stated, heteroxanthin is a methylxanthin and it is possibly identical with a substance obtained synthetically by Gautier. It has been suggested that heteroxanthin is formed in the

body by the splitting up of more complex xanthin bodies introduced with vegetable food. This theory of its origin finds support in the fact that it has never been found in the decomposition of nuclein, and in the further fact that caffeine and theobromine are excreted in the urine as methylxanthin.

The physiological action of heteroxanthin is identical in kind, but less in degree, with that of paraxanthin, which will be discussed later.

Methylxanthin, $C_6H_6N_4O_2$.—This substance is isomeric, possibly identical, with heteroxanthin. It has been obtained in the urine of dogs and rabbits, and in that of man after the administration of large doses of theobromine. Drinking large quantities of coffee also seems to give rise to this base in the urine; 24.6 per cent. of the theobromine fed to a rabbit appeared in the urine as methylxanthin. This base is soluble in hot water, from which it separates on cooling in the form of prisms or long needles. On rapid concentration of its aqueous solution it is thrown down in an amorphous state. The amorphous floccules, however, soon change to crystals.

Paraxanthin, $C_7H_8N_4O_2$.—This substance was obtained from the urine by Salomon in 1883. It has since been shown to be a constituent of normal urine, although it is present in very minute quantity. It has not been found in the urine of dogs or in that of leucocythæmic persons. Paraxanthin is sparingly soluble in cold water; more readily in hot water. It is insoluble in alcohol and ether. Its solutions are neutral in reaction.

As has already been stated, paraxanthin is isomeric with theobromine. It is, therefore, a dimethylxanthin.

Especial interest is attached to the physiological action of paraxanthin, inasmuch as it is believed by some to be the active agent in the causation of certain nervous disturbances, attention to which will be given later. From 1 to 2 mgm. of this substance, injected into the muscle of a frog, produces almost instantaneously a rigor-mortis-like condition of the muscle thus treated, with diminished reflex excitability. From 6 to 8 mgm. introduced into the dorsal lymph sac causes a gradual loss of voluntary motion as well as of reflex excitability. The rigor produced is more marked in the anterior extremities than elsewhere. Dyspnœa is an early and prominent symptom, but as soon as rigor sets in the respirations drop far below the normal, and may cease altogether for several minutes. In some animals the lungs are enormously dilated. The heart's action continues until death occurs. In mice, a tetanic condition is induced. The injection of 0.2 gm. into a guinea-pig weighing 500 gm. produced convulsions and death in half an hour. The same dose in-

troduced into the veins of a rabbit had no effect. The fatal dose for frogs, when given subcutaneously, has been found to be from 0.15 to 0.2 per cent. of the body weight. This indicates that this poison is more powerful than theobromine. In general, it may be said that paraxanthin destroys spontaneous muscular action, leads to loss of reflex excitability, and has little effect upon the heart's action until the latest stages.

Carnin, $C_7H_8N_4O_3$.—This substance was obtained in 1871 by Weidel from meat extract. It has also been obtained from fresh meat, from yeast, and from urine. Carnin forms a white, crystalline substance which when completely dry looks like chalk. It is very sparingly soluble in cold water, readily soluble in boiling water, crystallizing from the latter on cooling. It is insoluble in ether and alcohol. Its solutions are neutral in reaction and bitter to the taste. Physiologically carnin seems to have but little effect. It is stated by Brücke that when taken internally it causes some irregularity in the action of the heart.

Episarkin, $C_4H_6N_2O$.—This base was obtained by Balke from the urine in 1893. It is practically insoluble in water. It is readily soluble in dilute hydrochloric acid and on evaporation of this solution the hydrochloride forms in needles. With silver nitrate it forms a precipitate which is insoluble in nitric acid, but readily soluble in ammonia. It is easily distinguished from adenin and hypoxanthin by its insolubility in cold water. No definite statements can be made concerning the chemical constitution or the physiological action of this base.

Cytosin, $C_{21}H_{30}N_{10}O_4+5H_2O$.—This substance was obtained by Kossel and Neumann by decomposing adenylic acid by heating with twenty per cent. sulphuric acid in a sealed tube at 150° C. It was also obtained by the action of water on adenylic acid at 170° C. Cytosin is easily soluble in hot water, from which it separates on cooling. It forms crystalline salts.

Gerontin, $C_5H_{12}N_2$.—This base was first isolated by Grandis in 1890. It has repeatedly been found in a crystalline form in the cells in the liver and kidneys, particularly of old dogs. This base is an isomer of cadaverin. It forms in needles which are readily soluble in both water and alcohol. It possesses a strong alkaline reaction and responds to the general alkaloidal precipitants. Physiologically it exerts a paralyzing action upon the nerve centres and heart ganglia. Five-tenths of a milligram suffices to kill frogs.

Spermin, C_2H_5N.—This base was first obtained by Schreiner in 1878 from semen. It has also been found in the testicles of the bull, in various organs of leucocythæmic persons, and also from the sur-

faces of anatomical specimens kept under alcohol. Poehl found it in the testes, ovaries, breast, thyroid, pancreas, and spleen. It has also been reported as a constituent of the cultures of the cholera bacillus. However, this last statement needs confirmation. Spermin has long been known under the name of the crystals of Charcot-Neumann or those of Leyden. These crystals consist of the phosphate of spermin. They have been found in the sputum in cases of emphysema, in the bronchial discharges in acute bronchitis, in the blood and spleen of leucocythemics, and in the normal marrow of bone; also in the secretions from the nose and in fæces, as well as in semen.

Spermin, as a free base, is obtained by decomposing the phosphate with baryta and evaporating the filtrate, which on cooling yields crystals. From alcohol, spermin readily crystallizes. It is soluble in water and in alcohol; practically insoluble in ether. When heated on platinum foil, it gives off thick white fumes with a weak ammoniacal odor.

The attention of medical men has been especially called to spermin on account of the statement that it forms the active principle of the Brown-Séquard testicular fluid. Poehl states that it acts as a tonic on the nervous system. Further than this, nothing of professional interest is known concerning this base.

Leucomaïns of the Kreatinin Group.

The researches of the celebrated Italian toxicologist Selmi stimulated others to study not only the ptomaïns, but also alkaloidal bodies found in fresh tissue. Guareschi and Mosso were among the first to detect the presence of alkaloidal bodies in fresh tissue. When extraction of such tissue was carried out without the use of acids, only very minute traces of an alkaloidal body, possibly cholin, could be obtained. But when acidified water was used, other alkaloidal substances appeared in the extract. Schulze obtained a base, to which he gave the name arginin, and which has the formula $C_6H_{14}N_4O_2$. This substance was first found in the sprouts of lupin, and it was soon found to bear a close resemblance to kreatinin. Later, arginin was found in various tissues of the body from which it can be extracted with boiling hydrochloric acid. Horn yields 2.25 per cent., gelatin 2.6, conglutin 2.75, albumin 0.8, dry blood serum 0.7, casein 0.25 per cent. of this substance.

Drechsel has obtained two interesting bases. These are lysatin, $C_5H_{13}N_3O_2$, and lysatinin, $C_6H_{11}N_3O$. These may be obtained by decomposing gelatin, horn substance, and other proteids, with hydro-

chloric acid. These three bodies may be looked upon as important sources of the nitrogenous bases found in animals and plants. In 1869 Liebreich discovered an oxidation product of cholin in normal urine. This substance is probably identical with betaïn. In 1880 Pouchet found, in urine, allantoin, carnin, and an alkaloidal base which was not present in quantities sufficient to admit of a determination of its composition. Gautier has studied quite exhaustively the leucomaïns found in fresh muscle, and he has succeeded in isolating several compounds which will be mentioned later. Some of these substances are credited with possessing an intensely poisonous action, and if this be the case it is evident that any undue accumulation of these substances in the system may give rise to serious disturbances. The amount of these bases present in the daily urine is very small, so small indeed that we may look upon the traces found in this excretion as having escaped oxidation in the body. According to Gautier, there is constantly going on in the animal tissues of the body a cycle of changes consisting of the formation of leucomaïns and their subsequent destruction by oxidation. Should anything interfere with their destruction they may manifest poisonous effects. To the physiological chemist these bodies are of special interest on account of their possible relation to the formation of kreatin and kreatinin in the muscles. In these leucomaïns, as well as in those of the uric-acid group, hydrocyanic acid plays a very important part in their molecular structure. What the function of this cyanogen group is, so far as the physiological activity of the tissues is concerned, we do not know positively, although recent researches seem to show that the site of the cyanogen formation lies within the nucleated cell and is intimately connected with the functions of the nuclein molecule. Many of the bases obtained by Gautier were found in quantities so small that neither their chemical composition nor their physiological action could be studied with any thoroughness. We shall confine our statements to a few of the most important of these substances.

Crusokreatinin, $C_5H_8N_4O$.—This substance differs in its composition from kreatinin by a molecule of HCN. Both in its crystalline form and in its markedly alkaline reaction, as well as in some other properties, it seems to be closely related to kreatinin. This relationship, together with its golden-yellow color, induced Gautier to give it the name which it bears.

Xanthokreatinin, $C_5H_{10}N_4O$.—This is the most abundant of muscle leucomaïns. It forms in sulphur-yellow crystals, consisting of rectangular plates, resembling those of cholesterin. It is soft and talc-like to the touch. It possesses a slightly bitter taste, and when boiled with alcohol it gives off the odor of acetamide, though ordi-

narily in the cold it has a slight cadaveric odor. On the application of heat, this base gives off the odor of roasted meat; it carbonizes in part and yields ammonia and methylamin. Solutions of this base are amphoteric in reaction. When given in fairly large doses it is poisonous, producing in animals depression, somnolence, and extreme fatigue accompanied by frequent defecation and vomiting. Monari found xanthokreatin in the aqueous extract of the muscles of a dog exhausted by exercise, and also in the urine of soldiers tired out by a march of many hours.

Amphikreatin, $C_9H_{19}N_7O_4$.—This substance is slightly soluble in boiling water, from which it crystallizes in yellowish-white prisms, possessing a slightly bitter taste. It is a weak base and forms salts with the mineral acids. Nothing definite is known concerning its physiological action.

A Base, $C_{11}H_{24}N_{10}O_5$.—This substance crystallizes in colorless or yellowish rectangular plates which are tasteless, and which possess an amphoteric reaction. When heated with water in a sealed tube to 200° C. it is converted into a new base and urea, the latter being immediately decomposed into ammonia and carbonic acid.

Undetermined Leucomaïns.

Leucomaïns in Expired Air.—There has been considerable discussion concerning the nature of the organic matter contained in expired air. In 1870 Ransome estimated the amount of organic matter in expired air to be about 0.2 gm. per day. Later, it was shown by Uffelmann that the amount of organic matter in occupied closed rooms is increased in almost the same ratio as carbonic acid. Others have denied the existence of organic substances in the expired air. These have supposed that the only poisonous substance in expired air is carbonic acid. Others claim to have demonstrated that expired air from which all the carbonic acid has been removed is highly poisonous. Some years ago a series of articles by Brown-Séquard, D'Arsonval, and Wurtz on the poisonous properties of expired air attracted much attention. The first two of these observers found that the vapors exhaled by dogs, when condensed, and the aqueous liquid thus obtained was injected into animals death followed, generally within twenty-four hours. The symptoms observed were dilatation of the pupils, increase of the heart beat to as much as 280 per minute, and the slowing of the respiratory movements. Usually, paralysis of the posterior extremities was observed. Choleraic diarrhœa was invariably present in the animals experimented upon. In some there was a rapid lowering of the temperature from 0.5° to 5° C. Boiling

the liquid which had been formed by the condensations of the expired air, for the purpose of destroying any germs which might be present, apparently increased its toxicity. Wurtz stated that he had found in the condensed expired air a basic substance which forms a double salt with platinum, crystallizing in short needles. Later researches have thrown doubt upon all of these statements. In 1893 Ben obtained from 3,000 litres of expired air 100 c.c. of water of condensation. This liquid had a peculiar, not unpleasant, odor. It gave a distinct reaction for ammonia, but did not contain alkaloids. The organic substance in it amounted to 5 mgm., or, when calculated for the twenty-four hours, 15 mgm. From this and other experiments he concludes that the organic matter of expired air cannot induce acute intoxication. He believes that the dyspnœa observed in confined spaces is due to the lack of oxygen. Carbonic acid may give rise to dulness and headache, but the amount may be gradually increased and the effects will be negative so long as oxygen is not markedly decreased. The probabilities are that any poisonous substance or substances formed in the body when an insufficient amount of air is supplied are not eliminated from the lungs, but are retained in the body.

Leucomaïns in the Urine.—Many basic substances have been obtained from the urine. Some of these have been found in the urine of healthy persons and others in those suffering from various dieases. Space will not allow me even to mention all the leucomaïns that have been found in the urine. Attention will be given only to a few of the most important. In 1869 Liebreich found a substance which is probably identical with betaïn. In 1866 Bence Jones discovered in the urine an alkaloidal body which in sulphuric-acid solution possesses a blue fluorescence similar to that of quinine. In 1879 Thudichum announced the presence in the urine of four new alkaloids. The physiological action of these has not been studied. Pouchet has obtained from the urine several bases which are poisonous to frogs, producing paralysis, loss of reflexes, and arresting the heart in systole. This author also believes that the urine contains small quantities of pyridin basés analogous to those obtained in decomposing fish. Selmi examined a number of specimens of pathological urine and succeeded in obtaining from many of them basic substances, some of which were poisonous, while others were not. The urine from a patient with progressive paralysis yielded two bases, strongly resembling nicotine and coniine. He proposed that the basic substances found in the urine in disease be designated as pathomaïns.

The term urotoxy has been employed to designate the relative toxicity of the urine in various conditions. Lépine and Guerin found that

the extracts from pathological urine were more poisonous than those from the normal secretion. Villiers found basic substances, as a rule, in the urine of patients suffering from pneumonia and tuberculosis. In all of these experiments only extracts were employed, the base not being isolated in a degree of purity sufficient for analysis. Arslan found in the urine of two children with ankylostomiasis a base which induced an anæmic condition in rabbits. Boinet and Silberet isolated three bases from the urine of Basedow's disease, and found that these substances induced in animals effects similar to those observed in the disease. Dutto found in the urine of Addison's disease a base which behaved with reagents like cholin. Some writers consider this disease as an autointoxication. It may be mentioned in this connection that eclampsia is considered by Favre as ptomaïnæmia, whereas Bouchard regards it as due to the non-elimination of the normal poisons of the urine. However, it is more probable that it is due to perverted cell metabolism. Griffiths has given a long list of alkaloidal bodies obtained from the urine in infectious diseases; but there are many reasons for believing that his work is not reliable.

Omitting the mention of the special claims of investigators we may make the following general statements concerning the toxicity of the urine: It is a well-established fact that the urine of persons suffering from certain infectious diseases, such as cholera and septicæmia, is more poisonous than normal urine. These poisonous substances, whether they be bases or not, are probably generated in the body by the activity of the specific bacteria causing the disease. The excretion of the toxins of tetanus and diphtheria in the urine has been demonstrated. In the consideration of the toxins in the urine in infectious diseases it must not be forgotten that the poison as well as the specific germ may be present in the secretion from the kidney. It therefore becomes difficult to decide as to whether the toxin found in the urine is generated in the body or forms subsequently to the secretion of the urine.

The question of the toxicity of normal urine has been the subject of much controversy. Uræmia was formerly explained on the assumption that urea is poisonous and that the symptoms result from the retention of this secretion. Actual demonstrations of the toxicity of the urine were made early in this century by Vauquelin and others. On the other hand, disbelievers in the toxicity of the urea were not wanting. Thus, Frerichs maintained that death resulting from the intravenous injection of urine was due to suspended solid elements of the urine, that urea itself was harmless, and that it could by the action of a ferment give rise to the poison-

ous ammonium carbonate. Voit pointed out that potassium salts on account of their toxicity might play an important part in the production of uræmia. It can now be positively stated that normal urine does possess a certain degree of toxicity. It is more difficult to decide upon the nature of the poison. According to Bouchard, 30 to 60 c.c. of normal urine injected intravenously will kill a rabbit weighing 1 kgm. Hence a man weighing 60 kgm. and excreting per day 1,200 c.c. of urine would, if 50 c.c. are necessary to kill 1 kgm. of living matter, secrete enough poison to kill 24 kgm. of animal. Inasmuch as the amount necessary to kill 1 kgm. of animal is designated as one urotoxy, therefore in the above case twenty-four urotoxies are formed per day. The urotoxic coefficient is the number of urotoxies which 1 kgm. of man forms in twenty-four hours. Therefore in the case supposed above $\frac{24}{60} = 0.4$ is the urotoxic coefficient. The average normal coefficient is placed by Bouchard at 0.464. It follows, therefore, that an average man would, if the excretion of urine was stopped, be killed in fifty-two hours. In disease the urotoxic coefficient rarely exceeds 2 and seldom falls below 0.1.

According to Bouchard, five kinds of poisons may occur in the urine, producing narcosis, salivation, mydriasis, paralysis, and convulsions. The day urine, which is chiefly narcotic, is from two to four times more toxic than the sleep urine, which induces convulsions and is antagonistic to the former. The toxicity is independent of the density, since night urine is more dense than that secreted during the day. Bouchard ascribes the greater part of the toxicity to organic poisons, especially coloring matters, whereas potassium salts are regarded as a factor of less importance. Lépine also found that about 60 c.c. of urine sufficed to kill 1 kgm. of rabbit. However, he attributes much more importance to the inorganic salts, claiming that eighty-five per cent. of the intoxication is due to these substances. The remainder of the toxicity he believes to be due to the organic matter. Stadthagen also believes that from eighty to eighty-five per cent. of the toxicity of urine is due to the inorganic constituents, while from fifteen to twenty per cent. is due to organic substances. No one organic substance in the urine possesses this toxicity. Gautier has supposed that the urine poison is a proteid analogous to those in the venom of serpents. In the present state of our knowledge upon this subject, we may conclude that the poisonous action of normal urine is due to the sum-total action of inorganic salts, chiefly those of potassium, and the normal organic constituents, such as urea, kreatinin, etc. Increased toxicity of the urine has been observed by Surmont in atrophic cirrhosis, tuberculosis, and cancer of the liver, while on the other hand the toxicity was normal or subnor-

mal in hypertrophic cirrhosis, hepatic congestion, and in infectious icterus.

Leucomaïns in the Saliva.—According to Gautier normal saliva contains poisonous substances in small quantities, and these differ very much in their action according to the time of their secretion, and probably according to the individual gland in which they are secreted. He states that an aqueous extract of saliva dried at 100° C. is poisonous or narcotic in its effect upon birds. He claims that the saliva contains a basic substance to which the above-mentioned action is attributable.

The Relation of Leucomaïns to Disease.

The time for a scientific discussion of the autogenous diseases has not yet arrived. A volume might be filled with inferences. However, only a few demonstrated facts can be given. In discussing the relation of leucomaïns to disease, it will be necessary to give to the term leucomaïn a wider significance than that to which it has been restricted in the discussion of the chemistry of these bodies. We designate as autogenous those diseases which have their origin in altered activity of the cells of the body in contradistinction to those diseases which owe their origin to the introduction of foreign cells or foreign poisons. It is certainly true that if we should drink only chemically pure water, take only that food which is free from all adulteration and infection, and breathe the purest air free from all organic matter both living and dead, yet our excretions would contain poisons. It is true, I believe, that the excretions of all living things, plants and animals, contain substances which are poisonous to the organisms excreting them. In man, some of these poisons originate in the activity of those bacteria which are constantly present in the normal contents of the intestines. Strictly speaking, poisons thus formed are ptomaïns and not leucomaïns. However, good arguments might be advanced for classifying any diseases having their origin in the products of these bacteria among the autogenous affections.

Bouchard has shown that normal fæces contains a highly poisonous substance which may be separated by dialysis, and which when administered to rabbits causes violent convulsions. He estimates that the amount of this poison formed in the intestines of a healthy man each twenty-four hours would be sufficient to kill the individual if it was absorbed. Of course, we do not know that all of this poison or these poisons is formed in the intestinal tract. Some of it may be separated from the blood or lymph, some of it probably passes with

the bile into the intestines. It is a well-known fact that constipation is followed by a group of more or less disastrous symptoms depending upon the extent to which elimination is interrupted. Physicians recognize a form of fever due to non-elimination. As a rule, there is in these cases more or less headache, the tongue becomes coated, and the breath offensive. Such cases often speedily improve under the influence of a brisk cathartic. In surgical cases, when, on account of an operation, the patient must keep in bed, this fever of non-elimination frequently appears. The same is true in obstetrical cases. In these, an elevation of temperature often gives rise to great alarm, as the physician suspects septicæmia; but if the elevation of temperature be due to non-elimination, the fever rapidly disappears after free purgation.

The products of imperfect digestion may be absorbed and may give rise to serious disturbances. Even undigested egg albumen may to some extent at least produce these effects. Prior examined a case in which a boy, after eating sixteen raw eggs, had a high fever accompanied by the appearance of both albumin and hæmoglobin in the urine. Peptones and albumoses in large amount may reach the general circulation. That these substances are poisonous under these conditions is shown by the fact that when injected directly into the blood their toxic action is marked, the coagulability of the blood is destroyed, blood pressure is lowered, and when large quantities are used death speedily results. Brunton is inclined to attribute the lassitude, depression, sense of weight in the limbs, and dulness in the head, occurring in active men after meals, to poisoning with peptones and albumoses. He advises that such person should be placed upon a diet less rich in nitrogenous material. That peptone does find its way into the general circulation is shown by the frequency with which it is found in the urine. Moreover, albumosuria is more frequent than peptonuria. There is a rich field for investigation in the study of the physiological and toxicological action of the various products of digestion. Again, it is possible that the digestive ferments sometimes find their way into the blood in sufficient quantities to cause deviations from health. The older physiological chemists state that pepsin and trypsin are frequent if not constant constituents of normal urine; but their experiments were made without reference to the possibility of the ferments, which they found, being formed by the bacteria of the urine, and after carefully going over the literature of the subject I am not prepared to pass judgment on the truth of their statements. However, the fact that these ferments manifest a marked toxicological action when introduced into the blood is of great interest. Hildebrandt has reported some experi-

ments made by himself upon this subject. He finds that a fatal dose of pepsin for dogs is from 0.1 to 0.2 gm. per kilogram of body weight, when injected subcutaneously. Such injections are followed by a marked elevation of temperature, which he designates as ferment fever. The fever begins within an hour after the injection, reaches its maximum after from four to six hours, and may continue for some days. During the period of elevation of temperature, there are frequent chills. During the twenty-four hours preceding death the temperature generally falls below the normal. The symptoms accompanying the so-called ferment fever vary to some extent with the species of animal. Rabbits lose flesh, notwithstanding the fact that they continue to eat well. They become very weak, and death is preceded by convulsions. Dogs tremble in the limbs, become uncertain in gait, and vomiting, dyspnœa, and coma are followed by death. Section shows parenchymatous degeneration of the muscles of the heart, and slight changes in the liver and kidney. There are abundant hemorrhages in the intestinal canal, in Peyer's patches, in the mesenteric glands, and sometimes in the lungs. Thrombi are frequently found in the lungs, and in some cases in the kidneys. The action of these digestive ferments when thus administered on the coagulability of the blood is worthy of mention. At first there is a period during which the coagulability of the blood is greatly lessened, then follows a period of greater rapidity in coagulation, and it is in this latter stage that thrombi are formed.

That certain other febrile diseases are autogenous in origin, there can be but little doubt. They may be due to an excessive formation of poisonous substances in the body, or they may be due to insufficient elimination through the skin, bowels, or kidneys. As an example of fever of this kind, we may mention fatigue fever. After excessive and long-continued exercise there may be an elevation of temperature of from 1° to 3°. The appetite becomes impaired, and if at this period an opportunity for rest is at hand sound and refreshing sleep is impossible, the brain becomes excited and refuses to be at rest, the senses are alert, and all efforts to sink them in repose are unavailing. Fatigue fever is frequently observed in armies upon forced marches, especially if the troops consist of young men unaccustomed to service. Mosso has studied this fever in the Italian army. He states that in fatigue the blood is subjected to a process of decomposition brought about by the infiltration into it from the tissues of poisonous substances which when injected into the circulation of healthy animals induce malaise and all the signs of exhaustion. It has been suggested that in this decomposition of blood fibrin ferment is set free, and that it is the cause of the elevation of

temperature. Fatigue fever is often accompanied by chilly sensations, and frequently it is mistaken for malaria, and quinine is administered, but without good effect. Then there is the fever of exhaustion, which differs from fatigue fever only in degree. This is brought on by prolonged exertion without sufficient rest, and is especially likely to occur when the exercise is taken without sufficient food. The healthy balance between the formation and elimination of effete matter is disturbed, and it may be weeks before it is reëstablished—indeed, it may never be reëstablished, for some of these cases terminate fatally. The fever of exhaustion may take on a typhus form, delirium may appear, muscular control of the bowels may be lost, and death may result.

Rachford has made some most valuable contributions to our knowledge of the relation of leucomaïns to disease. He has pointed out and apparently established the fact that there is a migraine which is due to an excessive amount of paraxanthin in the blood. This leucomaïn is found in relatively large quantities in the urine after attacks of this headache. He also accounts in the same way for a certain form of epilepsy which he designates as leucomaïn epilepsy; also for a form of gastric neurosis and to a variety of asthma, due to the same poison. He has conducted some investigations concerning the relations of leucomaïns to chronic alcoholism, lead poisoning, and to uræmia. In some of these diseases he has obtained from the urine abnormally large amounts of paraxanthin, and by injecting this substance into mice and rats has induced symptoms similar to those of certain forms of epilepsy, and to the nervous symptoms of chronic lead poisoning.

As already stated, the scientific study of the relation of the leucomaïns to disease is yet to be carried out, and there can be scarcely any doubt that careful and thorough studies of this subject will lead to results hardly less important than those which have followed the demonstration of the causal relationship between bacteria and the infectious diseases.

INFECTION AND IMMUNITY.

BY

HAROLD C. ERNST,

BOSTON.

INFECTION AND IMMUNITY.

A COMPLETE study and summary of all the work that has been done in this field would be utterly impossible. In the following attempt at a statement of the series of experiments leading to the present position upon these points, much that is of value is of necessity omitted, and possibly, too, some work that is more deserving than that spoken of. But if this be the case, it is certain that no personal bias has been permitted intentionally to influence the selections.

The two subjects forming the heading of this chapter are inextricably interwoven in their experimental study, and their presentation may be made for convenience under two headings: first, the experiments leading to our present ideas upon infection, and the methods by which it may occur; second, the consideration of immunity, (*a*) natural and (*b*) acquired.

INFECTION.

Modes of infection, so far as the recent ideas are concerned, are well discussed by W. H. Welch, who takes the ground occupied by most modern observers that "there is now tolerable unanimity of opinion as to the meaning attached to the terms infection and infectious diseases. Most recent authorities understand by *infection* the condition produced by the entrance and multiplication of pathogenic microorganisms within the body. An infectious disease is one which is caused by the invasion and reproduction within the body of pathogenic microorganisms. To define an infectious agent as a specific poison capable of indefinite multiplication is only to express obscurely the idea just conveyed, for we know and can conceive of no poison capable of indefinite multiplication except a living organism. The analogies formerly drawn from the fermentation and the putrefaction of organic substances, and still preserved in the designation 'zymotic diseases,' have lost all force as an opposing argument since it has been shown that such processes are produced by living organisms. In the absence of any other probable, I may say even conceivable, hypothesis, to refuse to accept the doctrine of a contagium vivum as applicable to all infectious diseases because it has been demonstrated

only for certain of these diseases, is about as reasonable as to reject the law *omnis cellula e cellula*, because this has not been proven for every cell or every species of cell. This definition of infection cannot justly be limited to the bacteria or fission fungi. Most of the infectious agents yet known are certainly bacteria; but the plasmodium of malaria is an exception, and the probabilities are that other cases exist. Our means for demonstrating the bacteria are fairly satisfactory, but as much cannot be said of most of the protozoa, and it is perhaps because of this imperfection of methods of investigation that so many infectious diseases have successfully resisted efforts to discover their efficient causes. . . .

"To explain why, under natural conditions, some diseases, such as the exanthemata, are usually transmitted by contagion, other diseases, such as typhoid fever and cholera, only infrequently, and still other diseases, such as malaria, never by contagion, it is necessary to consider the channels by which the virus is eliminated, if at all, from the body. If, as in the case of malaria, the virus is not discharged at all from the body, then of course there is no possibility, under the conditions of nature, of the communication of the disease from one person to another. If, as in the case of cholera and of typhoid fever, the virus is discharged only by way of the fæces, then contagion is possible, but it is not likely to occur with ordinary care and cleanliness. If, as in the case of scarlet fever, measles, and smallpox, the virus is eliminated from the skin and adheres to thin scales of epidermis which can be readily transported through the air, then contagion is likely to be a common occurrence. It is not to be inferred that the mode of elimination of a virus is the sole factor in determining the degree of contagion of a disease. Of course other important factors must be taken into consideration, such as the degree of resistance of the virus to drying, the chances of its being conveyed into the air, its quantity, etc., as well as the degree of susceptibility which exists on the part of those exposed, and the portal through which the virus must enter in order to cause infection. This should be a more rational, fruitful, and satisfactory way of regarding the infectious diseases than to wander among the mazes of miasmatic, contagious, and miasmatic-contagious diseases, and to imagine that in some diseases the virus is eliminated in a potent state, and in others in a state requiring some subsequent transformation to make it potent.

"Wyssokowitch has shown that non-pathogenic bacteria injected into the blood of animals in a few hours disappear from the blood and are deposited in certain organs, especially the liver, spleen, and marrow of the bones, whence they also disappear, as a rule,

in a short time. They are not eliminated by the urine or any other secretion, and his experiments justify the statement that the specific germs of infectious diseases can be, and, in cases of recovery, doubtless often are, destroyed within the body; and, contrary to what many have believed, the kidneys and intestines cannot be regarded as important means of freeing the body from microorganisms which have gained access to the blood. When the specific microorganisms of an infectious disease are found in the urine or in the fæces, it may be inferred that the genito-urinary and the alimentary tracts respectively are the seat of some lesion produced by these organisms. These experiments justify also the inference that the specific viruses of infectious diseases are discharged from those free surfaces which are themselves the seats of the characteristic lesions of the disease, as for instance from the respiratory tract in pulmonary tuberculosis, lobar pneumonia, whooping-cough, diphtheria; from the skin in scarlet fever, measles, smallpox, typhus fever, erysipelas; from the intestines in typhoid fever, cholera; from the urethra or vagina in gonorrhœa or syphilis. For several diseases, however, there are no satisfactory data for determining in what manner the special poison is eliminated, as in cerebrospinal fever and relapsing fever. We are ignorant as to whether microorganisms may be eliminated by the breath, although it is a common notion that this occurs. In view of the experiments showing the difficulty with which microorganisms are detached from moist surfaces by currents of air, it seems improbable that they can be conveyed from the body by the breath. Of course if they were set free by the expulsive efforts of coughing, they might be carried on by the respiratory current, but it is at least very questionable whether in ordinary breathing particulate substances can be thus transmitted, and the evidence at hand is all against their being so transmitted.

"The general conclusions seem to be warranted that every infectious disease has its infectious element, but that whether or not that disease is likely to be propagated as a contagious one depends upon various circumstances, among which the mode of elimination of the virus from the body is of the utmost importance. The question of the reproduction of infectious microorganisms outside of the body, although it has not all of the significance sometimes attached to it, is nevertheless one of much interest to the medical profession in this country and in England, and it is not conceivable how there can still be distinguished authorities who deny that epidemics of typhoid fever or of cholera are ever attributable to drinking-water, and yet in Germany there are hygienists who are very strongly opposed to what they call the drinking-water hypothesis. It is doubtless true that we

are often too ready to accuse the drinking-water in an outbreak of typhoid fever, and at the same time if medical evidence is worth anything, there seems to be no room for doubt that many epidemics of typhoid fever have been at any rate started by contamination of a water-supply with the typhoid virus. Although as shown by Sedgwick's work for the Massachusetts State Board of Health, the contamination of a milk supply from an unsuspected source is as dangerous a means of transmission as any yet known. Meade Bolton has shown the important fact that most pathogenic microorganisms do not multiply in water sufficiently pure for drinking purposes; not only this, but if they do not contain spores most of them are destroyed in a very short time, varying from a few hours to days. These experiments are not opposed to the view that epidemic infection can occur through drinking-water, but only make it necessary to suppose that a single infection of the drinking-water with infectious organisms would not suffice for an epidemic lasting more than a few days. To keep up a long-continued epidemic by means of contaminated drinking-water there must be some communication between the water and some focus in which the disease-producing organisms are present in large numbers, or are multiplying. This is in harmony with the fact that repeatedly in epidemics traceable to the water, communications have been proven to exist between the water and cesspools, drains, privies, or other possible foci of infection. In considering water as a source of infection, one must remember that this can occur not only by drinking, but also by the use of the water in cooking, and in washing dishes subsequently used to contain food.

"As regards the means of transportation by which the agents of infection are conveyed from external objects to the body, the most important is believed to be the air by those who lay the most stress upon the influence of the soil in the spread of epidemic diseases. It seems probable, however, that too great a rôle has been assigned to the air as a carrier of contagion. The fact has already been mentioned that currents of air are incapable of lifting bacteria from moist surfaces. Naegeli has shown also that if bacteria be dried with their natural gelatinous envelopes or free albuminous substances, they are in much the same physical condition as insects attached to a surface by mucilage, and cannot be carried away by the air unless they are first converted into a dust-like powder. If it be furthermore considered that some bacteria are destroyed by complete desiccation, it is evident that these facts compel us to restrict within much narrower limits than most writers have done the importance of the air in the transportation of agents of infection. Still there remains evidence enough that the virus of some diseases, notably of malaria, and prob-

ably of yellow fever, may be and often is conveyed through the atmosphere. As infection through the air is something which we have no means of combating, it is encouraging to learn that this resistless fate has a narrower sway than we had been led to believe.

"There are many grounds for supposing that the chief means of infection are by actual contact in one way or another with the agents of infection. The conviction of the truth of this statement is borne in almost irresistibly upon one who has engaged extensively in the cultivation of microorganisms. I have kept for weeks at a time, side by side in a sterilized dish to which filtered air had free access, two watch-glasses, one containing a culture of the typhoid bacilli in beef tea, the other containing simply sterilized beef tea. During this time, notwithstanding its close proximity to the typhoid culture, the beef tea in the second glass remained perfectly pure, without a trace of contamination from its neighbor. Many illustrations of the same principle might be drawn from the work of a bacteriological laboratory. We study the exposed cultures of such pathogenic organisms as the anthrax bacilli, the cholera spirilla, the glanders bacilli, and run no risk of infection from these, so long as we do not come into contact with the cultures. There is one observation which we sometimes make in our laboratories in summer which is not without its practical bearings. This is the readiness with which microorganisms may be disseminated by flies and other insects. Upon the so-called plate cultures we can sometimes trace the devious wanderings of an insect by the colonies of microorganisms which it has planted in its course. The application of this experience to a possible means of transportation of the special organisms of infectious disease is too apparent to need further elucidation. There are of course thousands of ways in which we can inadvertently come into contact with sources of infection. This teaches us that it is an error to construct exclusive theories on infection, such as are expressed by the terms 'soil hypothesis,' 'drinking-water hypothesis,' etc. Of the various factors entering into the causation of infectious diseases none is more obscure than that designated predisposition, and yet this is a factor with which we must undoubtedly reckon.

"It cannot be said that the increase in our knowledge concerning the specific causes of infectious diseases has illuminated to any great extent what is meant by predisposition. Perhaps the most positive addition to our knowledge in this direction has been the demonstration of the importance of preëxisting diseases or lesions of structure in affording ready means of ingress and suitable conditions for the lodgment and growth of pathogenic microorganisms within the body. In this connection attention may be called to the experiments of

Wyssokowitch and of Prudden, which show the necessity of previous alterations of structure in the cardiac valves before they are adapted for the lodgment and development of the microorganisms which cause ulcerative endocarditis. Grawitz has shown that the bacteria of suppuration may be injected in large quantity into the healthy peritoneal cavity without doing any damage, but that they set up suppurative peritonitis if they meet these wounded tissues, stagnating fluids, or so-called dead spaces from which they are not readily absorbed.

"It may be well to say that possibly we are at present in the habit of assigning too great importance to predisposition as a factor in the causation of infectious diseases. It is such a convenient refuge that we are tempted to bury in its obscurity many etiological facts which we cannot readily explain. While I would not by any means ignore the importance of hereditary predisposition to tuberculosis, is it not probable that cases are often included in the category that do not belong there? When we think of the special dangers of infection to which the offspring of tuberculous parents are exposed from their youth upward, of the likelihood that a child will follow an occupation which has favored the development of phthisis in a parent, and of the frequency with which the concurrence of the disease in ancestor and descendant is mere coincidence, it is apparent that we are in danger of assigning to heredity a larger part in the causation of tuberculosis than it deserves."

Influence of Race.

The difference in susceptibility of different races of men to infectious diseases is very marked. Buchner, in discussing the influence of the pathogenic bacteria upon man, insists that a marked difference must be made between "ectogenous" infection (in which the bacteria can flourish outside of the body, the locality of the disease, and then pass into the body) and "endogenous" infection (in which the plant flourishes only in the diseased body, and passes from the diseased to the well). To the "ectogenous" infections belongs that disease spread over the whole earth, malaria, in all its forms—intermittent, remittent, pernicious, etc. So far as malaria is concerned, it seems to be unquestionably the case in Africa that the native population, and in particular the negro, has a peculiar resisting power as compared with the European; and indeed this is true also of another ectogenous disease, yellow fever. The opposite of this is true, however, of the "endogenous" diseases. All accounts show that the negro has a peculiar susceptibility to smallpox, although this disease is common in Africa, and the same thing is true in regard to pulmonary tuberculosis, to which infection negroes, Polynesian Maoris, and many

other uncivilized peoples are peculiarly susceptible. The mortality cannot be laid entirely to the door of bad living in these native races, which undoubtedly is greater than in Europeans. If their peculiar susceptibility to smallpox, tuberculosis, etc., can be attributed to bad living and generally unhealthy surroundings, the same thing should be true in regard to malaria and yellow fever. In other endogenous diseases, like measles and influenza, the relative susceptibility of the European is less than that of the colored. Beriberi shows its endogenous character by affecting natives more frequently than foreigners.

There appears to be a general law that Europeans have a relative immunity to the endogenous diseases, a relative susceptibility to the ectogenous, while the colored races, especially the negro, have directly the opposite characteristic. The relative immunity of the colored races to the ectogenous infectious diseases appears to be an inherited characteristic. So it is not remarkable that these races, in general of slight resisting power, should show a relative immunity to malaria and yellow fever, but a further conclusion is of the utmost importance as affecting European colonization, namely, that the European races cannot obtain a similar resistance to the ectogenous infectious diseases until after many generations in the same climate. So that, according to Buchner, the fate of the European in tropical climates could be predicted on theoretical grounds, and this has never been falsified by the actual occurrences. Many territories whose climate was good before, became malarious when the cultivation of the land was begun, and in hot climates turning over the soil seems often to set free the fever germs. To become acclimated is the only way to avoid the illnesses customary upon a change of climate, and this "acclimating" must go on through a number of generations and slowly, the final result very likely being an entirely new racial product. This process is probably illustrated in the case of the South-African Boers, who have apparently very widely departed in the course of their development from the racial peculiarities of the Dutch from whom they came.

This susceptibility of native races to special infectious diseases is also shown in the statistics collated by Matthews. The fact of the large mortality among full-blooded Indians being recognized (in 1880, being 17.74 in 1,000 for whites, 17.28 for negroes, 23.6 for Indians), the search for the reason of it was much aided by Billings' statistics. By these it appears that in 11 diseases the negro has a higher death-rate than the Indian, and that in 8 the Indian has a higher than the negro; these 8 are diarrhœal diseases, measles, scrofula, tabes mesenterica, venereal, and especially lung diseases. The mor-

tality in these latter among Indians is 286 in 1,000 deaths, but only 186 in 1,000 among negroes; and this difference is still more marked between the whites and the Indians, being for the former 166 deaths in 1,000. This susceptibility of the Indians to lung troubles is ascribed by Matthews to "contact with civilization." The Indians live either confined to very narrow limits or entirely free. The mortality from phthisis for those restricted in their movements is 184 in 1,000, for the free 373 in 1,000. These numbers are very striking, but not in accord with the general mortality of the disease. Matthews collected the mortality statistics of diseases of the lungs among the Indians in 13 States and Territories, and compared these with the general mortality from phthisis. He established by this means that the mortality from lung diseases was higher among the Indians living east of the Mississippi, and therefore longer in contact with civilization, while it was much lower among those living west of the Mississippi; and that this was far above the general mortality rate, even two or three times as great. Furthermore, the statistics for single years from 1875 to 1880, because of errors, give no certain results as to the general numbers of lung troubles among Indians on the same reservation. For these and other reasons the conclusion has been reached that lung disease among the Indians increases under the influence of civilization, and manifests itself as a disease that belongs to a foreign and more highly developed race, and that climatic influences have no effect upon it. At precisely what stage in the developmental civilization of the Indian this suseptibility to lung diseases occurs the author does not make perfectly clear.

Causal Relation of Microorganisms.

Dosage of Bacteria.—In the earlier investigations concerning the infectious diseases not so much importance was attached to the *size of the dose* of the bacteria as this has been later shown to possess.

Cheyne first called attention to the matter. His first experiments were made with the proteus vulgaris of Hauser, a pyogenic bacillus. A pure culture injected subcutaneously in a rabbit in a dose of $\frac{1}{10}$ c.c. produced death in from twenty-four to thirty-six hours; the blood and the organs contained very few bacilli. It is therefore probable that in animals rapid death following the injection of large amounts of this bacterium is due to the absorption of some toxic material secreted by it. If smaller doses ($\frac{1}{40}$ c.c.) be used, the result is an abscess of slow formation, to which the animal succumbs generally at the end of six to eight weeks; in smaller doses still the abscess is still more slow, and the animal ultimately recovers; and finally, there is no

effect whatever produced by the use of extremely small doses. Counts made with the aid of plate cultures showed that a perfectly harmless dose consisted of 9,000,000 bacteria or less; that an abscess resulted after injecting from 9,000,000 to 112,000,000, while a dose of from 225,000,000 upwards very rapidly produced death. The injection of a *single* bacillus of anthrax under the skin of a guinea-pig (an extremely susceptible animal) produced death, as did that of a single bacillus of mouse septicæmia (the count being made by means of plate cultures). A very few of the bacilli of chicken-cholera injected under the skin of a rabbit produce a fatal result, but if an animal more refractory be taken, like the guinea-pig, it is necessary to inject 300,000 bacteria in order to produce death, smaller numbers only produce a local effect, and a dose of less than 10,000 gives no result at all. Similar results were obtained upon using the bacillus of rabbit septicæmia in guinea-pigs, and the staphylococcus pyogenes aureus in subcutaneous injection; a large dose killed, a small one produced an abscess. The same thing was also worked out with the bacillus of sputum septicæmia, and the micrococcus tetragenus.

These results can be compared with those of Chauveau, who found that large doses of anthrax could overcome the immunity of Algerian sheep to this disease; and the work of Arloing, Cornevin, and Thomas, who demonstrated that small doses of anthrax produced only a slight disturbance with a resulting immunity; and that of Pasteur himself, who showed that the inoculation of extremely minute quantities of the cord of a rabid animal does not produce the disease. Cheyne came to the following conclusions: 1. The pathogenic dose of virus is in inverse proportion to the degree of susceptibility of the animal to the disease in question. 2. When an animal not especially susceptible receives an injection, the severity of the result is, in a certain degree, in direct proportion to the amount of the virus injected. 3. To a certain extent the period of incubation is in inverse ratio to the quantity of virus used. 4. In certain cases, small doses of the virus protect against the fatal effects of later and stronger doses. These conclusions hold to-day.

Inflammation.

The discussion as to the cause of inflammation has had much to do with the development of our ideas in general in regard to infection. It would still appear as if, for all practical purposes, inflammation with suppuration does not occur without the presence and activity of bacteria; that is to say, that by far the greater number of cases of such inflammation occurring in practice are the result of

bacterial growth. But this view does not accord with that taken by many writers.

Regarding inflammation as a process characterized by the formation of pus and having its seat in the capillaries, Sanderson shows that this is essentially the result of an injury done to the tissues by chemical agents of a certain intensity, and that the dictum of Weigert, "no suppuration without bacteria," is untenable. In fact he asserts that the proximate cause of inflammation is always chemical, and to justify this proposition he endeavors to show, first, that inflammation (that is suppuration) can be produced by chemical agents in the absence of microphytes, and, secondly, that when it is produced by microphytes the action is chemical. The second point he thinks is sufficiently established by a series of observations, extending over about eight years, made by a number of competent bacteriologists. The essential feature of these methods of experiment is to introduce sterilized irritant liquids, either subcutaneously or into serous cavities, using precautions to preclude the entrance with them of microphytes.

One of the first of the more exact investigations on the subject was that of Councilman, and consisted first in charging capillary tubes with the liquid to be experimented with, closing the ends hermetically, and then, after sterilizing the tubes and its contents, introducing it under the skin and closing the wound aseptically. After it had remained several days it was broken with the fingers subcutaneously so as to discharge its contents. Similar experiments were performed by Scheuerlein, who substituted fusiform for cylindrical tubes, and contrived to introduce the contained fluid very slowly into the subcutaneous tissue and the peritoneal cavity. The chemical substances used were very various—mercury, nitrate of silver, turpentine, croton oil, etc. Mercury was found to produce suppuration in the dog, but not in the rabbit. When injected hypodermically in the dog, each drop became the centre of a minute abscess. Silver nitrate in five-per-cent. solution produced suppuration in the dog, but not in the rodent. Ammonia failed to produce pus in any animal. Turpentine produced suppuration with great certainty in the carnivora. The action of croton oil was similar but inferior. In all these experiments the materials used were sterilized, and introduced with the most rigid antiseptic precautions, and the pus obtained was tested by cultivation, and cover-glass preparations were subjected to microscopic scrutiny. In every instance, provided the experiment was properly performed, the inflammatory exudation fluid was sterile. These experiments seem to show not only that suppuration can be brought about without the concurrence of microbes, but that the

readiness with which pus is formed depends upon conditions which belong to the animal rather than to the noxa. In the dog a sterile abscess can be produced with ease with such different agents as mercury and turpentine, but it is much more difficult to obtain the result in a rodent.

The other point in Sanderson's contention, that when microorganisms are directly concerned in the production of inflammation the mode of action and the proximate cause are still chemical, is based on the fact that not only in the case of the staphylococcus, but in that of many other micrococci, the symptoms that result from the presence of the microphytes themselves in the living organism can also be produced by the soluble chemical products of the vegetation. So long ago as 1878 Pasteur showed that cultures of the "microbe générateur du pus," which had been sterilized, were as capable of producing abscesses as living cultures were, and that the resulting pus was sterile; but it was not until 1887 that Grawitz made similar experiments with pure cultures of pyogenic microbes, particularly with the ordinary staphylococcus. Since then various other experimenters have investigated the subject in relation to this and other pus-producing microphytes, with the general result that in carnivora sterile abscesses can be produced with the same certainty by the introduction or injection of devitalized cultures of staphylococcus as by that of turpentine or mercury. In rabbits, when a Cohnheim's tube charged with such sterilized cultivation is used, the same phenomenon presents itself as if the tube contained croton oil, that is to say, leucocytes creep in at the end, die, and form pus.

Biotic and Toxic Agents.

From a consideration of the more recent accepted investigations as to the morbific agents in tuberculosis, typhoid fever, pneumonia, tetanus, and diphtheria, as well as in relapsing fever, splenic fever of animals, and inflammation or its characteristic result, suppuration, Sanderson is disposed to deduce two types of morbific action, viz., biotic and toxic. Biotic agents act mainly by virtue of their endowments as living organisms; toxic agents chiefly by virtue of the toxins which they produce. That is, the nexus between the morbific agent and the morbid process is in the one case dissemination, and in the other diffusion.

As to the causal relation between microphytes and the diseases they produce, it is necessary to bear in mind also the possible substitution under certain conditions of one species for another. Recent researches have furthermore taught that the toxicity of a disease-

producing microphyte is even more essential to its effects than its adaptability to a living nutritive medium. The question of *infection*, therefore, has become more and more chemical and less morphological. The employment of the bacteriological method is, however, none the less necessary, and the pathologist must continue to perfect himself in the technique that Koch has created. If the questions appear for the moment to be chiefly chemical, it is only that we have passed from the form to the substance, from the agent to the action. Our interest in microphytes is not as botanical species but as makers of toxins; and in toxins not as chemical compounds but as disease-producers. The contest in the organism between invading microphytes and the living elements of the invaded territory is not a hand-to-hand fight between tissue elements and microphytes (Metchnikoff), but one in which both act (so to speak) at long range, in which the weapons are poisons and counter-poisons, toxins and anti-toxins—words implying that the pathological endowments of these bodies are antagonistic. We have, on the one hand, products allied to modern proteids, to ptomaïns, or leucomaïns, on the other hand, the old vis medicatrix naturæ or vis protectrix, most recently designated as an attribute of the liquor sanguinis (Behring and Kitasato).

Influence of Season.

The influence of the time of year upon the appearance of infectious diseases has been worked out by many observers from statistical data. Almquist studied measles, typhoid fever, diphtheria, cholera, dysentery, malaria, cerebrospinal meningitis, smallpox, scarlet fever, whooping-cough, typhus fever, infantile diarrhœa, pneumonia, and bronchitis. They all seemed to have a more or less intimate relationship to the time of year. As a result of his work, he considers that diarrhœa, cholera, dysentery, and typhoid fever are summer-autumn diseases, diphtheria a winter disease, and pneumonia a spring disease, while the others range themselves with less certainty in one or the other of these groups. The way in which the time of year affects these diseases is not well determined, but the changes of the year, the outdoor temperature, the moisture of the air, the quality of the dwelling, and the manner of living, etc., may all be supposed to have some influence in this direction. Almquist thinks that the theory of the ground-water influence has had more put upon it than it can bear. Of course, all such points must be considered in any complete study of the influences bearing upon infection.

Fœtal Infection.

The transmission of the infectious diseases, as shown by Wolff, can theoretically occur by a *germinative* or conceptional infection, *e.g.*, an infection of the egg by pathogenic bacteria before the actual impregnation of the ovum, or during the act of impregnation by infected spermatozoa, or else by a placental or intrauterine infection of the fœtus during its development. His experiments were carried on with anthrax, vaccina, and variola. The experiments relating to the transfer of anthrax from the mother to the fœtus have led to entirely opposed results. On the one hand, a number of authors (Brauell, Davaine, Bollinger, and Koch) have come to a negative conclusion, while on the other hand Koubassoff, and lately Straus and Chamberland (who at first held that it could not occur) have seen reason to believe that a transmission of anthrax from mother to fœtus is, at least, not an impossibility.

Nine pregnant guinea-pigs and rabbits were inoculated subcutaneously with anthrax spores. The animals died of anthrax in times varying from thirty-six hours to three days. Twenty-nine of the young were examined for the presence of anthrax bacilli, and in not one did the microscopic examination demonstrate their presence; they were found in a large number of cases in the maternal placenta, never in the chorion. There were 156 cultures made from the internal organs of the 29 fœtuses, of which 150 showed no growth of anthrax bacilli, but 6 did. Lastly, from the organs of the 29 fœtuses, 29 control animals were inoculated, and of these, 3 (2 guinea-pigs and 1 white mouse) died of anthrax. Straus lays special stress upon the similarity of the results of all three methods of investigation —the microscope, cultures, and inoculation. In by far the largest number the results were negative, and the few positive results in the inoculation and culture experiments were ascribed to the probable accidental transfer of a minute portion of the maternal tissue with that of the fœtus. At any rate, the freedom of the fœtus from anthrax transferred in this way is unquestionably the most common condition. Whenever the transfer of anthrax infection from mother to fœtus does occur, there must be some special condition of the placenta or general system. The few positive results of Straus, Chamberland, and Koubassoff cannot be considered as conclusive since they were not constant, and since Koubassoff, moreover, confined himself to the microscopical examination of the tissues alone, and neither of the others carried out all three methods of investigation.

Wolff took into special consideration the points that might be

made against him, and studied therefore whether the age of the pregnancy, the duration of the infection, the structure of the placenta, or the condition of the blood could have any influence upon the transmission of the anthrax bacillus from the mother to the fœtus. He demonstrated by injection methods, in opposition to Koubassoff, that there is no direct vascular communication between the mother and the fœtus; and he further demonstrated that normally the placenta is impassable for unorganized bodies as well as for anthrax bacilli, and that when a passage of the latter to the fœtus does occur, some pathological alteration of the placenta must exist.

The second of Wolff's investigations upon vaccina is of extreme interest as well as importance. He attempted to settle this question by experiments upon human beings. His method was to inoculate pregnant women with pure humanized virus, and then to vaccinate the babies a short time after birth; if the infants were immune, this immunity could of course come only from their mothers; if not immune, of course they could have received no protective principles from their mother's blood. Twenty pregnant women in all were inoculated; in four cases there was a full, in nine cases a modified, and in three cases no reaction at all; in the nine cases it was not a first, but a second vaccination, the first having been followed by typical vesicles. Seventeen of the babies from the mothers that showed reaction were vaccinated on from the first to the sixth day after birth, and all seventeen showed typical vesicles with marked reaction of the skin at the site of the vaccination. These observations seemed to show pretty conclusively that a vaccination of the mother conveys to the fœtus no immunity to vaccine inoculation, and, of course, therefore, none to variola infection, and that the placenta does not permit the passage of the vaccine contagium from the maternal blood to that of the fœtus. The occurrence of complications, such as syphilitic alterations of the placenta, and pyæmic or septicæmic changes following vaccination, accompanying which it may be found that the fœtus has acquired a certain immunity after the mother has been vaccinated, cannot be considered; and besides no well-authenticated case of this sort has been recorded.

Finally, as regards variola, in such cases as have been reported, it seems probable that the fœtus has been infected by means of some special hemorrhage, or by actual contact in passing through the vaginal canal; such an explanation would seem to be much more rational than to consider that the infection passes through the placenta in opposition to the experimental evidence here offered. This question has been taken up by many others, of course.

Maffucci compresses a great deal of information into the ten

pages of his article. The experiments consisted of two series, the first to determine the behavior of an already developed embryo towards an infection, and the second the development of the embryo after the infection of the egg. The microbes of chicken cholera, pneumonia, anthrax, tuberculosis of fowls, and mammalian tuberculosis, and the toxic products of the two latter were employed. In the experiments on chicken's eggs, the bacteria were introduced in the egg albumen during or before the brooding began, and the eggs were examined at different lengths of brooding time, some of them being left until hatched. When inoculation was made at the beginning of the breeding time the bacilli first entered the embryo after ten days; the course being through the allantois and not the area vasculosa. In inoculation after fourteen days' breeding, after the complete formation of the allantois, the bacilli could be found in the embryo after a few hours. So long as the embryo lived, the bacilli grew either in the albumen or in the embryo; the embryos were not susceptible to an infection, although the living embryo might contain sufficient bacilli to kill a full-grown animal; in the embryonal tissue they could either be destroyed or their virulence might be diminished.

The infection may appear after the hatching (tuberculosis of fowls). Fowl tuberculosis may, a long time after the hatching, develop in the liver, may heal in this situation, and may make its reappearance in the lungs. The embryo may destroy the bacilli of fowl tuberculosis, or may become marasmic under its influence and may die of this affection a long time afterwards without at any time manifesting any trace of tuberculosis; the same result may be observed if the toxin of the bacillus be injected instead of the living cultures. The destruction of the bacilli by the embryo does not make this insusceptible to another infection later. The destruction of the bacilli was found to be in the liver, due to attacks by the leucocytes and endothelial cells, a process seen only in the last days of the breeding time. The bacilli that remained in the albumen retained their virulence, for control animals inoculated with the albumen died, while those inoculated with the embryonal tissue or with cultures made from the embryonal tissue remained alive.

In the second series, Maffucci experimented upon rabbits by the injection of bacilli of tuberculosis in the jugular vein; his results were very remarkable. The young of pregnant mothers show, he said, the bacillus within four (!) hours after the inoculation of the mother. The development of the bacilli in the placenta could not be determined after fifteen days; they circulated in the placental blood, did not become localized, and were extremely difficult to demonstrate. The organs of a fœtus from a mother made tubercu-

lous contained living and virulent bacilli within forty-eight hours after the jugular inoculation. Many of the guinea-pigs inoculated with the fœtal organs became tuberculous and died of marasmus, as when inoculated with dead tubercle bacilli. Rabbits born of tuberculous mothers did not show any tubercles six months after birth; after this time tubercles could be found in the liver and lung, but bacilli could not be found in these tubercles. All the observations showed that embryonal tissue behaves very differently from fully developed tissue.

Dohrn, also, formulates his opinion in regard to the hereditary character of syphilis, after long observation of the placenta, ova, and the abortions of syphilitic mothers, that "syphilis is only transmitted by conception, and the spermatozoa as well as the ovum are alike in this respect." If the ovum is healthy at conception, it will remain so in spite of a syphilis subsequently acquired by the mother; and the healthy mother will not be infected by the syphilitic fœtus in the uterus. The syphilitic poison is arrested by the placental wall whether from the fœtus to the mother or from the mother to the fœtus.

The general belief seems to be that bacteria themselves cannot pass through a healthy placenta to the fœtus, but that bacterial products may do so.

Wolff and Fischl also make interesting contributions to this subject from an experimental point of view. Wolff shows that the freedom of the fœtus from anthrax in an infected mother is the rule. In 47 cases examined, 39 of the fœtuses were entirely free from any indication of the disease; so much so is this the case that even when the placenta was found to be filled with the bacteria the chorionic membranes were absolutely without any. Since the placenta builds a wall against their entrance, it must be supposed that when they do gain such entrance some pathological lesion must have occurred. Similar results have been reached by other observers. Malvoz, in 32 fœtuses from 4 different mothers infected with anthrax, never once found bacilli by microscopical examination; and out of 163 cultures only 3 times were bacilli found. Rosenblatt, in 9 fœtuses from 5 mothers dead of anthrax, found bacilli in only 2 out of many hundred sections, and in 76 cultures only 5 colonies; Birch-Hirschfeld, Simon, and Lubarsch all came to the same conclusions, namely, that the anthrax bacilli were either entirely absent in the fœtal organs, or else were present in exceedingly small numbers. In the hemorrhagic character that anthrax has is to be found the best explanation of fœtal infection, namely, through a placental hemorrhage, as was demonstrated in one case of hemorrhagic anthrax in a guinea-pig, in the internal organs (liver) of whose fœtuses were found anthrax bacilli,

by culture, microscopical examination, and inoculation experiments. At the same time, it is not all kinds of hemorrhage that will result in fœtal infection, as was shown, at least so far as crushing the placenta is concerned; for after such procedure no one of sixteen fœtuses showed any infection either by the microscope, culture, or inoculation. Only such hemorrhage seems to be effective for this result as is similar to the capillary injury produced by the anthrax bacilli. Fœtal infection with anthrax has not yet been observed in man.

Further researches were made upon fœtal infection with the staphylococcus pyogenes aureus; pregnant rabbits were inoculated with this bacillus in the jugular vein. After a time the rabbits died and staphylococci nodules were found in the kidneys; in the fœtuses the staphylococci were found more often than was the case with the anthrax bacilli; nine out of fifteen gave positive results. Hemorrhage of the placenta, whether produced by crushing, needles, or setons, only resulted in making more of the fœtuses show the presence of the bacilli; so that for this organism any kind of bleeding seems to be favorable for the entrance of the bacteria.

Wolff took up anew the question of the transmission of tuberculosis to the fœtus, by inoculating pregnant animals, and animals before pregnancy occurred, with tuberculous sputum, in the latter case to obtain, if possible, a tuberculous infection of the ovum. Out of forty-two fœtuses of rabbits and guinea-pigs not one showed any tuberculous change, no matter how highly tuberculous the mother was, and the microscopical examination of the internal organs was entirely negative. Wolff injected males as well as females, the former in the testicles, and although the power of procreation was thus diminished, he succeeded in obtaining fœtuses conceived by them; but none of the results gave any tuberculosis. In only one case, that of a mother with many tuberculous nodules in the inner organs, was it possible with an emulsion of the liver of the two fœtuses to inoculate guinea-pigs; they died with tuberculosis of the internal organs, although the microscopical examination of the two fœtuses was entirely negative so far as showing any bacilli of tuberculosis was concerned. Sanchez-Toledo reached negative results in the careful examination of sixty-five fœtuses of tuberculous mothers. Gaertner was, however, more fortunate; of eighteen mice with tuberculosis of the abdomen, he found two tuberculous young; of nine canaries with abdominal tuberculosis of the parents two were tuberculous; and from six pregnant rabbits injected in the veins of the ear with bacilli of tuberculosis, one of the young was tuberculous. Experiments with females impregnated by males with tuberculous testicles gave Gaertner negative results; of such, six young rabbits, thirteen young

guinea-pigs, and four ova were non-tuberculous. Wolff also reported the cases of three tuberculous mothers dead with the fœtus in the uterus, and here also the most careful microscopical and inoculation experiments were without result. That an occasional transmission of the tuberculous bacilli from mother to fœtus may occur seems to be demonstrated by a monograph of Birch-Hirschfeld; but this occurrence must be of the rarest, and the bacillary transmission of tuberculosis by this means plays a most insignificant part.

Puerperal Autoinfection.

In line with these studies are those of which the works of Ahlfeld, Thorn, and Steffeck may be taken as samples. The former relates two cases by which he seems to establish the occurrence of a true self-infection of the mother after childbirth. The first case was that of a woman who had severe hemorrhage and chills after a fall. After five days she gave birth to a five-months' fœtus; afterwards she had high fever, which was treated with disinfecting fluids after the removal of the placenta and the membranes. The blood from the placenta gave no odor, and that from the membranes and vulva only the usual odor. He thinks this was the result of "a putrid infection" due to the toxic action of something in the nature of a ptomaïn, and in no way to the entrance of bacteria. The second case was a somewhat similar one with high fever and rapid pulse in a woman who had aborted, and was due, according to Ahlfeld, to a ptomaïn poisoning. In neither of these cases, however, is there any record of a bacteriological examination, so that the evidence upon which to base so extremely important an assertion is to the last degree incomplete.

W. Thorn takes the opposite ground to these conclusions of Ahlfeld as to the possibility and frequency of occurrence of self-infection in childbed. Most of the cases heretofore investigated from a bacteriological point of view have been so investigated after the birth has occurred, and the condition of the genitals before birth was not known, and so also many times the cases have been those of women who have given birth to the child somewhere else than at the hospital, and the condition of the surroundings was entirely unknown. He does not think it right to conclude that in the vagina and cervix of a healthy woman there are always bacteria that can at a moment's notice produce independently an active puerperal septicæmia. Normally the cavity of the uterus contains no bacteria after childbirth, while the vagina and cervix harbor numerous saprophytic parasites that cannot spontaneously assume a toxic property. Rarely the vagina and cervix contain also pathogenic bacteria, the explanation of whose presence is not easy; but this presence must be considered to

be abnormal, and an explanation must be sought if one is not at hand. Bacteria occurring in the vagina under normal conditions are for the most part saprophytic, and also such occur as may upon favorable nutrient media produce toxic ptomaïns, or pathogenic bacteria occur in the vagina and cervix which are found to be of attenuated virulence; but it is also unquestionable that such bacteria may under the conditions of childbirth find a favorable medium for their development. But infectious pathogenic bacteria find their way into the genital canal of healthy women only under abnormal conditions, and are undoubtedly brought there from other sources.

Steffeck's investigations consisted in a number of animal inoculations with the secretion from the genital canal. The method pursued was to obtain secretion from pregnant women as nearly as possible unexamined, and after securing the secretion to transfer it to a suitable nutrient medium, and then employ the culture in the inoculation of animals. The microorganisms found in the resulting abscesses, pus, or general infection were compared with those found in the original secretion, and finally these microorganisms were injected, and the results, when used singly or together, were noted. The secretions came mostly from unexamined pregnant women, by which as nearly as possible the occurrence of contamination was avoided. One-half to one cubic centimetre of this secretion was mixed with 4 c.c. of sterilized physiological salt solution, and after microscopical examination the mixture was placed upon agar-agar, sometimes as a streak, sometimes as a plate culture. After three days in the incubator the varieties of bacteria found were studied in pure culture. Rabbits were used as the experimental animals; the secretion in the above dilution was injected subcutaneously, and the examination was made upon the following day. In half of the cases, sometimes before and sometimes after the inoculation, the temperature was taken in the rectum so as to establish an average, and a rise of 0.5° C. (nearly 1° F.) was considered to be pathological.

In cases in which abscesses followed, cultures were made from the pus. If an animal died, the examination was made as soon as possible after death, and cultures were made from any pus and affected organs that were found, as well as from the heart's blood; sections were also made after hardening and were examined for bacteria microscopically after Gram's method of staining. Pure cultures were made from the bacteria found in the secretions as well as in the affected animals, and after a sufficient growth for them, the water of condensation in the agar cultures was mixed with 3 c.c. sterilized salt solution, and of this 4 to 5 c.c. was injected subcutaneously; if there followed any abscesses or general infection, these were also examined bacteriologically.

In all there were twenty-nine examinations of secretions made in this way, and it was determined that when any results occurred they were due to the presence of the staphylococcus pyogenes albus or aureus or to that of the streptococcus pyogenes. In the twenty-nine experiments with injection of the secretion, there resulted seven cases of abscess and five of general infection which ended in the death of the animal. In all of the positive cases, one of the three bacteria named was found, but never in the seventeen negative ones. In the twenty-nine secretions, the staphylococcus pyogenes albus was found nine times, the staphylococcus pyogenes aureus three times, and the streptococcus pyogenes once.

Of the positive cases a vaginal examination had been made in only two before the secretion was obtained for observation, the other ten had not been examined; in eight cases the woman was an untouched primipara, in four cases a multipara. In the negative cases, an internal examination had been made in four cases; seven of the women were multiparæ, seven primiparæ. The death of the rabbit followed the injection of the secretion in five cases. The same bacteria were found in all the abscesses and in the heart's blood of the experimental animals that were found in the secretions. After the injection of pure cultures there followed in two cases severe disturbance lasting for sixteen days, in three cases abscesses which contained only the original bacteria, and in two cases there was a general infection that resulted in the death of the rabbits.

The conclusion was reached that the pathogenic bacteria that may occur in the genital canal of unexamined and healthy women are the staphylococcus pyogenes albus and aureus, and the streptococcus pyogenes.

The results of the injection of bacteria-free secretions were also noted. About 1 c.c. of secretion was diluted in a sterile test-tube with 4 c.c. of sterile salt solution, and was then placed three times for twenty minutes in the steam sterilizer; then it was injected subcutaneously into ten different rabbits.

The result of these ten experiments were absolutely negative. In the ten secretions of this series, the staphylococcus pyogenes albus was found twice, and once the streptococcus with it. The conclusions seem to be that the staphylococci (pyogenic) as well as the streptococci may be the cause of the so-called self-infection in puerperal sepsis. It also seems that the possibility of a self-infection in labor lies here; but that it takes place only when something pathological has occurred during the labor. As a preventive, a prophylactic disinfection of the genital canal is suggested.

Infection of New-Born Infants.

Fischl demonstrates that in infants in the first week of life, which are born in lying-in institutions or received in foundling asylums, suppurative infection not rarely occurs under the form of an acute or subacute gastroenteritis or a capillary bronchitis and lobular pneumonia. That these affections should be grouped among the "septicopyæmias" appears certain from the close resemblance of their bacteriological and anatomical appearances to the septicopyæmic infectious diseases. The histological characteristics consist in the necrosis of the specific cells, interstitial inflammation, and a tendency to hemorrhage; the microscopic changes in the mucous membrane of the intestinal tract are not in proportion to the severity of the affection, and not rarely are entirely absent. Cultures also in such affections show in the various organs, and especially in the lungs, pure cultures of one or more of the staphylococci or streptococci, which may be shown by experiments upon animals to be of the highest degree of virulence. The post-mortem diagnosis of this affection rests upon the relatively slight alteration of the mucosa of the digestive tract, upon the presence of marked degenerative changes in the abdominal glands, ecchymoses in the serous surfaces, suppuration of the inflammatory nodules in the lungs, and miliary abscesses, as well as upon the results of bacteriological examinations. The source of the infection is without any doubt to be especially sought in the air of the sick-chamber; the channel of entrance is by the navel wound or vessels, by the food sometimes, or else through the respiratory tract, the latter being the most frequent. In addition to these septic infections of infants with gastrointestinal or pulmonary symptoms, there also occur acute dyspepsias, as well as genuine pneumonias with specific bacteriological results, which, however, are rare and of a favorable prognosis.

Infection through the Intestinal Tract.

Passing from the genital to the intestinal canal, Korkunoff, among others, takes up the suggestion of Emmerich (on the ground of animal experiment) of the possibility of bacteria passing through the healthy intestinal wall. Many of the best observers take the opposite view of this matter, for example, Koch and Pasteur. The first said as early as 1877 that anthrax spores could enter the system not only through the skin but through the intestinal canal as well. To prove this he fed mice with the organs (spleen, freshly dried and dried a long time, and blood) of sheep and rabbits dead of anthrax, and found

that the mice remained free from anthrax. Similar results were obtained with rabbits, and on the ground of these experiments Koch concluded that an intestinal infection with bacteria, at least in the case of these animals, was not possible. Pasteur and Toussaint made many feeding experiments, and one of their animals died of anthrax. Further experiments with plants (thistles, ears of corn, barley) calculated to irritate the mucous membrane, showed a marked increase in the number of deaths in their feeding experiments with anthrax, and they came to the conclusion that for an intestinal infection to occur there must be an injury to the mucous membrane. Koch and his pupils, Gaffky and Loeffler, experimented with sheep, and reached the conclusion that anthrax bacilli died in the stomachs of these animals, and the spores passed on into the intestinal canal and produced the general infection. They later experimented with small quantities of dried spores, and reached the conclusion that in such cases the spores did not produce any result; sometimes with small quantities of spores the animals were taken ill very slowly (six to twenty-two days after infection). In such cases it is also possible that a secondary infection occurred by the excrement being mixed with the animal's food. In general, Koch and his school came to the conclusion that anthrax spores in large masses produced as certain infection in the intestine as when introduced under the skin. Similar experiments with other animals, as guinea-pigs, rabbits, and mice, did not give constant results.

Buchner got very different results in his feeding experiments with anthrax spores (very few fatal results following unless large masses were used) from those seen in his inhalation experiments. Falk found that anthrax bacilli might be taken into the intestine without result, but that spores fed to animals usually gave positive results.

Orloff concerned himself with the entrance of the staphylococcus pyogenes aureus into the tissues of the living animal (as in osteomyelitis, endocarditis ulcerosa, etc.), and sought to introduce them by feeding and by inhalation into healthy and unhealthy animals. For feeding, he made use of a mixture of oats and cultures of these bacteria; the feeding was continued for from one to fourteen days, and the animals supported it well for from one and a half to three months. The blood of such animals gave no cultures, but the intestinal contents among other bacteria contained the staphylococcus pyogenes aureus. Similar results were obtained after irritation of the digestive tract. Orloff considers that the epithelium of the digestive organs is the best protection against the entrance of bacteria, that an injury to this is necessary for their entrance to the circulation, and that thence they are distributed after the manner of an embolus.

Flügge considers, on the basis of the experiments of Wyssokowitsch (with the staphylococcus pyogenes aureus, bacillus indicus, and spores of the bacillus subtilis), that microorganisms cannot pass into the circulation through the mucous membranes of the respiratory tract or of the intestinal wall so long as these membranes are intact; but if this is no longer the case, they pass on to the next lymph gland. Flügge shares the opinion of Koch as to anthrax bacilli, that they cannot pass through an uninjured intestinal membrane, although it is probable that spores can do so. Baumgarten rather favors the idea that the microorganisms enter by the way of the intestines (especially in case of spontaneous anthrax), as he holds the opinion that their entrance through the respiratory tract is at the best problematical. Furthermore, he thinks that certain animals have a special predisposition to infection in this or that way; for example, neat cattle are very little susceptible to anthrax inoculation, but easily die from feeding with anthrax spores; mice, rabbits, and guinea-pigs behave in the opposite way. In general, most feeding experiments give negative results. The only exception is with anthrax, and here the observations of different observers vary greatly. The fallacy in these experiments lies in the fact that it is not possible to prevent the entrance of bacteria in other than the intended ways.

Korkunoff considered that the most rational way to investigate this interesting question was to study the intestinal contents themselves, and he experimented in various ways by feeding mice, guinea-pigs, and rabbits with different bacteria (Emmerich's Naples bacillus, anthrax, and chicken cholera). These were introduced by means of the stomach sound, or in food (white bread or softened biscuit); sometimes the stomach fluids were neutralized with soda. The dose usually employed was a third of a test-tube filled with biscuit and four to eight anthrax cultures (on potato or agar-agar). Cultures of the Naples bacillus were made on gelatin, of chicken cholera in bouillon. With the latter, when they contained a large number of bacilli, the biscuit was moistened directly without sterilizing; and the infectiousness of the cultures mixed in this way was tested by subcutaneous inoculation in control animals. Korkunoff also used organs (liver, spleen, kidney) from animals dead of anthrax by beating up small pieces with distilled water and then passing through gauze, putting the fluid thus obtained directly into the stomach. His experiments in this way upon rabbits and white mice gave no constant results. The guinea-pigs fed with the Naples bacillus all lived, with the exception of one that died by chance; all those fed with chicken cholera died. So he came to the conclusion that positive results could be obtained only by feeding with chicken-cholera bacilli (in rabbits), and that feeding

with other bacteria gave no regular results. It should also be said that sometimes positive results do not give absolute conclusions. As he could not get enough sheep (animals that according to Baumgarten are especially fit for feeding experiments) he used white mice, which according to his experience also have a peculiar susceptibility to feeding with anthrax. He carried on his experiments in the following way: he took three to seven mice that had fasted from eight to twelve hours, and gave them all pieces of biscuits (rusks) mixed with anthrax spores; after a time a second supply was fed to them, and after a certain time the animals were chloroformed, and the stomachs and intestines were hardened in seventy-per-cent. alcohol. In this way he obtained the intestines of eighteen mice (from five to eighteen hours after feeding) which were cut in sections and stained after Gram's method. In neither the intestinal walls nor the lymph glands (solitary follicles or Peyer's patches) were either anthrax bacilli or their spores observed, but on the free surfaces of the mucous membrane there were many bacilli to be seen, so that the conclusion could be drawn that these bacilli had developed from the spores that had been fed in the first instance. In other experiments animals died with anthrax, but here other sources of infection (such as the respiratory tract, etc.) were not closed; by the use of the stomach tube these sources of error are excluded. If these experiments can be applied to other animals they support Koch's assertion that anthrax can be communicated by feeding in sheep; since Pasteur reached different results with sheep, Korkunoff was tempted to believe that the conditions in sheep are the same as in white mice. In general, he considered that an infection through a sound intestinal mucous membrane is not possible. Entirely different results, however, were observed in rabbits fed with cultures of chicken cholera, in which every animal died, with the demonstration of the bacilli in the stomach contents afterwards (as masses by good double staining, or a single stain of the bacilli). According to Korkunoff's idea the infection occurs by means of a disturbance of the epithelium (necrosis) and after the removal of this material an entrance into the blood current. In general, he reaches the conclusion that an infection by the intestines can occur only from those bacilli that have the power of destroying the epithelium of that organ, and that the bacilli of chicken cholera belong to this class. *Not* of this class are Emmerich's Naples bacillus, the normal intestinal bacteria, anthrax bacilli and their spores (unquestionably for guinea-pigs and white mice), staphylococcus pyogenes aureus (Orloff), bacillus indicus, and the spores of bacillus subtilis, and staphylococcus pyogenes aureus (Wyssokowitsch). As to the other pathogenic bacteria, their properties

are not known, and experiments with them are of interest and importance.

In opposition to these conclusions, L. Beco thinks that he has demonstrated that the invasion of the blood and internal organs by the bacteria of the intestines occurs during life in a large number of individuals. Furthermore, it is not possible to look upon this phenomenon as anything specific, that is to say, peculiar to certain bacterial diseases that have their special seat in the intestines.

What is the practical value of these conclusions?

In concluding their memoir, Wurtz and Herman say that in spite of finding the bacillus coli so frequently in the organs at autopsy, it by no means follows that this bacterium must therefore be accepted as the cause of the maladies, or the cause of death. This conclusion we have strengthened by showing, both by clinical and experimental evidence, that the bacillus coli, no matter to what organs it may be carried by the blood current, develops after the death of the host, and may obscure the associated species. A recent observation of Charrin and Veillon is confirmatory in this direction; but there is more. Even if the infection of the deep organs by the bacillus coli, as shown at autopsy, occurs in most cases, if not in all, during life, yet there is considerable weight in the conclusion of Wurtz and Herman that "it is not possible to rest solely upon the presence of the bacillus coli in the blood and the internal organs, even though demonstrated before death, as evidence of the causal relationship between this organism and the disease." Flexner's work on terminal infections seems, however, to point to the opposite conclusion.

Infection through the Lungs.

Studies as to the possibility of infection through healthy skin and mucous membranes have naturally been concerned with the lungs. Buchner's research concerns itself with two sets of experiments, viz., (1) the inhalation of dry powdered anthrax spores, and (2) the inhalation of moist powdered anthrax rods and spores.

Anthrax spores were first mixed with materials which could be finely powdered (charcoal, chalk), were carefully dried, and then scattered in a closed room in which were white mice. In twenty-four cases death from anthrax occurred in from one to three days, after the animals had inhaled this powder from one-half to two hours. The number of animals experimented upon was larger than this, showing therefore that the breathing of such powders is not of necessity followed by anthrax. Of course the objection to these experiments could be made that the infection did not occur by the lungs, but by

the skin or intestinal canal. This was disproved by numerous control experiments with poorly dried powders in which virulent anthrax spores were mixed. Often after such experiments the animals were covered with the moist powders containing spores, and yet in only one case did anthrax develop. Many direct-feeding experiments were also tried with dried anthrax-spores, in which the results were directly opposed to those of Koch, showing that mice *could* become infected with anthrax by the intestinal canal, but only if the spores were introduced in large masses. In these cases it was very definitely shown that the fæces of the mice were extremely virulent, and that the greater part of the spores was passed unchanged. That not nearly so many spores were necessary for the infection by the lungs as by the intestines was shown by causing ten mice to inhale a definite amount of the spore powder, and ten others to eat three times the amount of the same spore powder. Of these animals, all ten of those that inhaled the powder were attacked with anthrax, but not one of those that ate the powder; so that the infection through the lungs seemed to be well determined. These results Buchner regards as directly opposed to those of Flügge and Wyssokowitsch, both of whom consider that lung or intestinal infection always occurs through the blood, the intervention of which is not necessary according to these results. To demonstrate that there occurs a direct passage through the intact mucous membrane of the lungs, those bacteria have been investigated which have their primary seat in the lung tissue, such as the bacillus of tuberculosis; the results obtained with the anthrax bacillus would be worth much more if every other possibility and explanation were shut out.

The experiments were carried out in two ways: in the first, anthrax spores were mixed with an easily drying powder, and this powder was then passed into a tightly closed chamber; in the second, bacteria-containing fluids (anthrax spores and rods, chicken-cholera bacilli, etc.) were sprayed in very finely divided form in the chamber. This method of breathing in the bacteria suspended in the air imitates sufficiently well the natural method, but permits the suspicion that some of the resulting infections came from swallowing the bacteria, and not through the lungs. Care was taken on this point by special-feeding control experiments, and by direct microscopical examination of the lung infection. The method of moist powdering deserves especial mention. The animals were not attacked by the bactericidal spray directly; the spray was first sent into a glass chamber, from which it passed out into the animal box as a very fine filmy vapor, which vapor at the same time was demonstrated to contain large numbers of the bacteria. In this

way, of course only a very small amount of the moist bacteria powder could reach the lungs; since the amount of the fine vapor was only 0.2 per cent. of the fluid used, if this amount was 40 c.c., then 0.2 per cent. would be only three drops, which was all that got into the box at all. Furthermore, the animals were exposed but once, and then only for from thirty to forty-five minutes. The capacity of the breathing-box was fifty litres, and the box held more than one animal at a time (from three to ten guinea-pigs, rabbits, and mice). With such precautions, the results were extremely exact. In all (in both kinds of experiments, moist and dry) there were 140 inhalation experiments; of the animals 96 were killed in from two to four days by the expected infection = 68.8 per cent.; 70 animals were *fed* as control experiments; of these 7 died = 8.9 per cent. The feeding experiments were mostly made with the same material that was sprayed into the inhalation chamber, so that the control animal always received in the intestinal canal many more bacteria than did the inhalation animals. Even so, only 8.9 per cent. were affected, and even this number is too high, for, as is shown by experiments of Koch, Gaffky, and Loeffler, large amounts of spores are necessary for infection by this method.

Calculation seems to show that the animals received at least 30,000 more spores in the intestines than were taken in by inhalation. The exactness of the results was well demonstrated by a special experiment. Forty-two cubic centimetres of anthrax-spore fluid was dried in forty minutes, and six guinea-pigs were placed in an inhalation chamber holding fifty litres. Only 0.21 c.c. of the mixture was introduced into the chamber as a vapor, and after the inhalation the guinea-pigs were absolutely dry; they were perfectly lively on this and the following day. But forty-eight hours after the inhalation two, and towards the end of the second day the four others died of the most acute form of anthrax. Section showed the lungs as well as the intestines to be absolutely normal, but under the microscope the lungs and spleen were found to be as full of bacilli as they are in an animal which has been inoculated subcutaneously. No trace of the channel of entrance of the infection could be found; and if one had relied upon the anatomical examination alone, the affection would have been regarded as spontaneous anthrax. All other inhalation experiments with anthrax spores confirmed these results. In guinea-pigs this method of infection was as certain as subcutaneous injection, or even more so, the number of spores used being so much smaller.

Next, the animals subjected to these inhalation experiments were killed after various periods of time with chloroform, and their lungs were examined by plate culture as to their anthrax contents. More than twenty animals were examined after this method; and always the

lungs, after the inhalation, were found more or less rich in anthrax bacilli; these counts also showed an increase in the number of bacilli proportionately to the time which had elapsed after the inhalation, which of course indicates an increase within the lungs, although this conclusion is not necessarily absolute. Careful microscopical study of sections from these lungs showed a number of interesting facts, namely, that the infection in individuals progressed with varying rapidity, and that there was a distinctly *first* stage of beginning infection of the lungs. In preparations from a mouse killed with chloroform twenty hours after inhalation, there appeared numerous small collections of bacilli (twenty to twenty-five), sometimes within, and sometimes without the alveolar walls; and since only dried spores were introduced, it is certain that these bacteria must have come from the growth of these spores, and that this growth occurred in the lung. This was seemingly confirmed by the fact that no bacilli were in the capillaries, and so they did not come from somewhere else; this was also shown by the freedom of the spleen from bacilli (in the shortest cases) as demonstrated by plate cultures, and also by the carbon particles in the borders of the alveoli which acted as carriers of the bacteria. It was also to be observed that the intestinal infection occurred much more slowly than that by the lungs. The animals fed with the maximal amount of the spore mass died at the earliest in four or five days; the inhalation animals, on the other hand, usually infected with extremely small amounts of the spore mass, died as a rule in from two to three days; so that it would seem quite clear that the mechanism and conditions of infection must in the two cases be very different. The arrangement of the bacilli in the collections spoken of persisted even in the later stages of the lung infection.

Sections of the lungs of a guinea-pig killed with chloroform twenty-three and a half hours after the inhalation of anthrax spores showed only here and there collections of anthrax bacilli, while the greater part of the lungs was entirely free from them; but these collections contained hundreds of bacilli, and there was one thing in especial to note, namely, that by far the greater number of these bacilli were contained in the interior of the capillary vessels. Thus it would appear that the blood was invaded within twenty-three and a half hours of infection, while the spleen remained entirely free. This preparation showed the successive steps of the process of infection directly under our eyes, and furnished a direct and certain witness of the possibility of the passage through the surface of the lung of an agent of infection. As to how this entrance may occur, there are two possible ways, viz., one by means of the lymph channels, the

other through the capillary walls. The two modes of entrance are not incompatible, and both may occur, but general observations and an examination of the specimens in these experiments point to the passage through the capillary walls, as what occurred here at least. The interval between the appearance of the small extracapillary collections and that of the large and for the most part intracapillary masses was too short for the bacilli to have passed into the lymphatics, then into the glands, thence to the blood, and finally to have produced the collections in the lung. Any other explanation is difficult, although certainly an entrance through the bronchial glands is possible; for the lymph glands are a certain filter only for lifeless particles, carbon, etc. (Arnold), and saprophytic bacteria. Pathogenic bacteria can pass through these obstacles, but only because of their vital activity, not mechanically. And besides, this passing through takes a long time, so that the rapid appearance of the bacteria in these cases can be explained only by a passage through the capillaries. This passage occurs not by any mechanical violence, but through the same spaces in the capillary walls that are opened by leucocytes and blood corpuscles in the case of inflammation, and represents in the case of bacteria, as in that of leucocytes, an active effort on their part; it is for this reason that the lifeless particles and saprophytic bacteria are found in such numbers in the bronchial glands, but never in the capillaries.

As regards the active character of the passage of the bacteria there is to be stated this conclusion, that the greater the irritation of the lung tissue the less the chance of a passage of the bacteria into the lungs. This is demonstrated by the great differences seen between inhalation experiments with anthrax bacilli and those with spores. In the former case the animals died very quickly, in thirty-six to forty-eight hours, and examination of the lungs showed a very different condition of affairs from that found when spores had been used; there was, namely, a tremendous serofibrinous hemorrhagic pneumonia. The sections presented a most instructive picture; the alveoli were filled at times with fibrinous exudate, then with cell elements, and at times with skeins and snarls of anthrax rods and threads. Most striking was the fact that in spite of this tremendous infection of the lungs, the general infection was almost nothing. The spleen contained almost no bacilli, and the complete freedom of the capillaries and larger blood-vessels in sections of the lungs was very noticeable. This marked difference between this and the conditions of spore infection may perhaps be explained by the fact that, the spores being in a condition of latent existence, produce at first no chemical irritation, and grow slowly and only at widely separated places, so that

they do not easily produce any generalized irritation; while, on the other hand, the entrance at the same time of many living rods into the lungs produces an intense general irritation, both by their growth and by the chemical products that result therefrom. Spore inhalation, therefore, produces an intense and rapid general infection without any marked local changes, while rod inhalation produces on the contrary an intense local affection without any marked, indeed with very slight general infection. The reason for this latter condition is to be found in the active character of the passage through the capillary walls; the inflamed lung may be open for a passive passage, but it offers an absolute resistance to the active passage of the bacilli. This is analogous to the results of Ribbert-Lahr with the staphylococcus pyogenes aureus, and explains the negative results of Flügge and Wyssokowitsch, and especially those of Hildebrandt, who reached the conclusion that the inflammatory condition of the lung walls was of very little consequence so far as the passage of bacteria was concerned.

The infectious elements that are fitted for the passage through the intact lung wall are undoubtedly only those that are blood parasites, for these have the power of passing through the capillary spaces, but no others can do so; to this class belong the bacteria of anthrax, chicken cholera, rabbit septicæmia, and hog cholera. With all of these, positive results were obtained from inhalation. With anthrax analogous results were obtained in the case of cattle and sheep, and these results may serve to explain the cases of spontaneous (so-called) anthrax in these animals, in which the idea of an entrance by the lungs has been hitherto ruled out, and also the metastatic appearances in cases of intestinal infection that have not been heretofore clearly explained. Spontaneous cases of intestinal anthrax appear to have occurred, but it is not at all clear that this is the explanation of them. In human beings the spirilla of relapsing fever and the plasmodium of malaria are to be included. In both cases the possibility of an infection by the lungs is apparent. Tuberculosis and glanders bacilli are not blood parasites, so that in these cases the possibility of a direct passage through the capillary walls does not exist, and the inhalation of the bacilli of tuberculosis is followed by a localized infection only, which is later followed by the generalized attack upon the other organs of the body. The bacilli are taken from the primary nodules through the lymph channels to the secondary ones and thus into the blood. Two experiments with the glanders bacillus showed that the primary infection of the lungs did not occur, while at the same time the spleen was full of the bacilli; in this case the bacilli went directly to the spleen by way of the lymph channels.

The microbe of erysipelas and the cocci of suppuration occupy a middle place, but they are in no sense true blood parasites, and a direct passage into the blood current of the lungs has not been observed; it appears that a slow passage through the lymph channels is the probable condition. It is not possible to determine this point in rabbits since they are not susceptible to these bacteria, and since also the passage by the lymph glands occurs only by active efforts; this affords an explanation of the negative results of Flügge and Lahr with the staphylococcus pyogenes aureus.

Typhoid and cholera bacilli are also not blood parasites, although the typhoid bacilli may be found in the capillaries; but it is not known from this alone whether it is possible for them to pass directly through the capillary walls of the lungs; animal experimentation can show nothing on this point, since animals are not susceptible to typhoid fever. As regards cholera still less is known, since the spirillum is not found in the blood at all. Cultures upon sterilized blood serum of rabbits show an easy growth, but nothing can be inferred from this so far as the behavior of the microbe in man is concerned.

Chemotaxis.

The influence of chemotaxis on infection is very well discussed by Massart and Bordet. As our knowledge of the life of the bacteria becomes more complete, microbian infection becomes a more and more complex phenomenon. At the beginning of these studies infection was considered to be a necessary result of the introduction of the bacteria (pathogenic) into the animal economy, but since then many modifications have made their appearance. The same bacterium may be pathogenic for certain species, and entirely inoffensive for others. The same species of animal may show races that are susceptible to a given bacterium, and others that are entirely insusceptible. Certain bacteria may be so attenuated in their virulence that they produce absolutely no effect when introduced into animals, or they may even make these animals capable of resisting the attack of the most virulent cultures. An analogous immunity may be secured by the introduction of sterilized bacterial products.

Experiments have also been carried on to determine the means set in motion by the animal to protect itself against the bacterial attack; phagocytosis and the bactericidal condition of the fluids of the body play the principal rôle in this direction.

Predisposition to Infectious Diseases.

Lastly, a species of animal that is refractory to a certain bacterium may, under the influence of certain causes, become susceptible to the attack. This modification constitutes the "predisposition to the infectious diseases."

Among the causes that increase natural or acquired susceptibility to disease are (1) the introduction of products secreted by the species of bacterium inoculated; (2) the introduction of the products secreted by another; (3) the exposure of the animal to conditions unfavorable to its existence, or the production of traumatic lesions; (4) the introduction of certain definite chemical substances; (5) the introduction of anæsthetics.

1. The introduction in the body of the animal of products secreted by the bacterium inoculated. Roger showed that after injecting into an animal (veins of a rabbit) the fluid pressed from the œdematous muscles of an animal dead of symptomatic anthrax, the rabbit became extremely susceptible to the disease. Bouchard succeeded in producing pyocyanic disease in the rabbit with very small doses, after having injected intravenously a filtered culture of the bacillus pyocyaneus. Vaillard and Vincent demonstrated the same thing with the tetanus bacillus, also showing that the animals never died when the bacillus was introduced alone. Herman obtained suppuration in the rabbit with small doses of the staphylococcus pyogenes albus, after having injected the watery extract of cultures of this bacterium. The observations of Courmont and of Rodet and Courmont gave results that were very similar to these. The first showed that the previous injection of the products of a tuberculous culture facilitated very much the subsequent infection with this bacillus, and the latter showed that the favoring action of the products of the staphylococcus pyogenes albus persisted for at least three months. In experiments in which the substances secreted by the bacteria are injected into animals it is well to practise the injection where this material will pass slowly into the general circulation. When the inoculation of a bacterium that is non-pathogenic to the animal experimented upon is made in the anterior chamber of the eye, it often happens that the animal succumbs, while it would have resisted the inoculation perfectly if it had been made elsewhere. This is so for symptomatic anthrax in the rabbit, according to Roger, and for pure anthrax in the pigeon, according to Metchnikoff. Bacteria injected into the anterior chamber find themselves for a certain time independent of the phagocytes, and they elaborate

at their ease the products that are spread broadcast throughout the system.

2. Introduction into the body of the animal of products secreted by another bacterium (microbian association). When two different bacteria are associated or when, after having injected the sterilized culture of one, we inject a second living bacterium, various results present themselves. Sometimes nothing especial is to be seen; which is what happens when a sterilized or living culture of the bacillus fluorescens putidus is injected and followed by small doses of the bacillus of blue pus. At other times it may be seen that such an injection acts favorably upon the organism, and enables it to resist better the pathogenic bacterium.

Lastly, and this is what interests us most, the introduction of harmless bacteria or their products may so influence the living tissues that they may become susceptible to attacks to which they were insusceptible before. Roger produced death in rabbits in which he had injected living or sterilized cultures of the bacillus prodigiosus at the same time as the bacillus of symptomatic anthrax, and the same result upon the injection of cultures of the pyogenic staphylococci and the proteus vulgaris. Monti succeeded in killing animals by old and attenuated cultures of pyogenic streptococci, of the staphylococcus pyogenes aureus, and of the pneumobacillus, provided only that he injected simultaneously a culture of the proteus vulgaris. Bouchard considers furunculosis in many cases due to the resorption of the substances secreted by the bacteria of the digestive canal, and he says that antisepsis of the canal arrests the disease. According to Vaillard and Vincent the injection of the bacillus prodigiosus in the rabbit makes this animal susceptible to the bacillus of Nicolaier.

Lastly, experiments show that white mice, which are insusceptible to the pyocyanic disease, will contract this malady after the introduction into the peritoneal cavity of $\frac{1}{40}$ c.c. of a sterilized culture of the bacillus prodigiosus.

3. The exposure of the animal to conditions unfavorable to its existence, or the production of traumatic lesions. It is sufficient to produce strong contortion of the abdominal muscles by means of an electric current in a guinea-pig, according to Nocard and Roux, and then to inject an attenuated virus to have the animal succumb to a dose of symptomatic anthrax culture entirely harmless under ordinary conditions. Platania after introducing Friedländer's bacillus into the trachea of the guinea-pig produced an aseptic lesion of the pleura and of the lung, and demonstrated that the animal is much more susceptible to this microorganism under these than under perfectly sound conditions. Charrin and Roger demonstrated that

white rats become much more susceptible to symptomatic anthrax or bacterial anthrax when fatigued by being made to run in a turning wheel. The chicken can be made susceptible to anthrax when cooled as shown first by Pasteur, and then by Wagner. Platania, after placing the pneumobacillus in the trachea, put the animals in a cold atmosphere, and found that they died of pneumonia. According to Charrin, cooling diminishes the resistance of the guinea-pig to the pyocyanic disease. The influence of hunger has been studied by Canalis and Morpurgo, who demonstrated that pigeons succumbed very easily to anthrax when enfeebled by hunger; bleeding also renders an animal much more susceptible, as demonstrated by Serafini, who found that the injection into the trachea or the pleura of Friedländer's pneumobacillus produced no effect unless the animal (dog) had been or was subjected to a copious bleeding. Arloing cites experiments made by Rodet with the anthrax bacillus; sheep inoculated in the ear succumb much more readily after having been bled than before.

Finally, there is an alteration which produces a susceptibility to the infectious diseases just as do contusions, that is, section of the nerves. All text-books upon ophthalmology cite cases of keratitis coming on after an injury to the trifacial, but the first experimental researches were made by Charrin and Ruffer. They severed the sciatic nerve of one side in a guinea-pig, and injected in both thighs the same quantity of a virulent culture of the bacillus pyocyaneus. An infectious tumor appeared on both sides, more marked on the side of the severed nerve. In the rabbit, section did not appear to favor this infection. Roger studied this same question. He removed from one side in the rabbit the superior cervical ganglion, and inoculated in the two ears the same quantity of a culture of the streptococcus of Fehleisen. For the first three days, the ear on the side on which the vessels were paralyzed was extremely œdematous, and the erysipelas was much more marked than on the other, but after that time the appearances changed, and the injured ear resumed its normal appearance, while the other became covered with pustules, and even became partially sphacelated. The experiments of Herman were even more complete and sharply defined. After he had resected a portion of the sciatic in rabbits, and the wound of operation had cicatrized, he injected into the veins cultures of the staphylococcus pyogenes albus; the observed arthritis, abscesses, and osteomyelitis were almost exclusively localized in the limb that had been operated upon. The experiments of Féré are of great interest; he vaccinated hemiplegic persons upon both arms; as they had been vaccinated but a few years before no characteristic vesicles appeared, but nodules of false vac-

cine developed with a very marked preponderance upon the paralyzed side.

4. Introduction into the animal body of certain definite chemical substances. According to Arloing, Cornevin, and Thomas, lactic acid increases the virulence of the bacillus Chauvæi; Nocard and Roux have demonstrated that the acid acts, not upon the microbe to increase its activity, but upon the tissues to lessen their resistance; acetic acid, lactate of potassium, chloride of potassium, and dilute alcohol produce the same effect; to cause the death of the animal it is necessary to inject at the same time in the same muscle the hurtful substance and the virus. Roger has obtained the same result by the injection of trimethylamin. Vaillard and Vincent gave tetanus to the rabbit by injecting lactic acid at the point of inoculation of the tetanus bacillus. Everybody knows that in debilitating diseases like diabetes, suppuration is extremely apt to attack the subject; and Bujwid has shown that the intravenous injection of glucose determined the presence of the suppuration at the point of inoculation of the pyogenic staphylococci. So, too, Leo gave an experimental diabetes to rats and mice by the injection of phloridzin; and in this way he took away from rats their immunity to anthrax, and from mice their resistance to glanders. Various authors have repeated these experiments with different results. Herman injected in the subcutaneous cellular tissue of the rabbit 1 c.c. of a three-per-cent. solution of carbolic acid; an hour afterwards he inoculated the animal at the same point with a dose of a staphylococcus too weak to produce any result under ordinary circumstances, and obtained an abscess; the use of a one-per-cent. sublimate solution gave a much less marked result.

5. Introduction into the animal body of anæsthetic substances. Platania produced anthrax in dogs, frogs, and pigeons by injecting with the cultures, curare, alcohol, or chloral; Wagner also produced anthrax in chickens by the use of chloral.

These numerous facts make it possible to assert that the injection of bacterial products and of certain definite chemical substances, and the exposure of the animal to abnormal conditions of existence as well as to the action of anæsthetics, diminish the resistance of the animal economy to the invasion of the bacteria.

It now remains to determine by what means the different factors act in the production of this diminution of resistance to the invasion of the bacteria. To explain these influences, two theories have been successively advanced by Bouchard. Before entering upon them it is necessary to state the actual condition of our knowledge of the chemotactic properties of the leucocytes, for it would seem to be

demonstrated that this matter of irritability of the white corpuscles plays a preponderating part in the diminution of immunity.

For some years it has been known that certain substances contained in bacterial cultures produce a purulent collection at the point of inoculation. Grawitz admits that certain products of the staphylococcus pyogenes aureus play a part in suppuration, and he demonstrates further that cadaverin produces an abscess when introduced into the cellular tissue of the dog. Scheuerlein also showed that solutions of cadaverin, putrescin, sterilized cultures of the staphylococcus, and even a putrefied sterilized maceration of the flesh of the rabbit could produce suppuration without bacteria. So far as the products of the staphylococci are concerned these observations have been confirmed by Christmas-Dirckinck-Holmfeld, Karlinski, and Steinhaus. The latter obtained purulent collections with dogs after the injection of bacillus prodigiosus, bacillus pyocyaneus, and bacillus anthracis. Leber isolated from cultures of the staphylococci a crystalline substance that he called "phlogosin," that possessed the property of attracting the leucocytes. He emphasized the analogy of this attraction with that determined by Pfeiffer for the spermatozoids of cryptogams in the presence of certain chemicals. Pekelharing introduced under the skin of the frog gun-cotton impregnated with a culture of the anthrax bacillus; after a few hours a large number of leucocytes had worked their way into the interstices of the cotton; this experiment was the first designed to demonstrate directly the attraction possessed by certain bacterial products for the leucocytes.

The irritability of these cells was studied by Massart and Bordet by placing capillary glass-tubes filled with living or sterilized cultures of various bacteria in the peritoneal cavity of frogs; the following day these tubes were filled with leucocytes. This cellular migration is modified or arrested upon anæsthetizing the animals. Gabritchewsky made a large number of the same sort of experiments upon the frog and the rabbit. The conclusion that they all reached was that the substance attracting the leucocytes was dissolved in the culture medium.

Buchner took up the question anew, with the same general idea of experimentation by the introduction in the tissues of capillary tubes containing the fluid to be tested; but instead of using culture media Buchner employed a protein obtained by treating the bacteria themselves. In this way he was able to demonstrate that the proteins extracted from various bacteria, and in particular the bacillus of Friedländer and of the bacillus pyocyaneus, acted as energetic excitants of the leucocytes. He is tempted to assert that the culture

fluid itself does not possess the property of attracting the leucocytes; but it is difficult to assent to this opinion in view of the experiments of Gabritchewsky, and of Massart and Bordet on the result of the use of filtered cultures of the bacillus pyocyaneus.

These various researches demonstrate that certain bacterial products have the power of attracting the leucocytes; these are then carried into contact with the bacteria that are attempting to attack the organism; they can destroy them at once before the bacteria have had sufficient time to elaborate the products that might be harmful in large quantities. Metchnikoff's work makes it more and more probable that immunity rests, in great part at least, upon the phagocytes; in order that they should be most effective, it is necessary that the white corpuscles that constitute especially the most active of the phagocytes should be collected in one place, the threatened points of the economy. And it results from Bouchard's experiments, as well as from those of Massart and Bordet, that in animals in which the immunity is lessened by some of the predisposing causes the leucocytes have lost their power of transporting themselves in the neighborhood of their enemies. Bouchard inserted under the skin of a rabbit a Hess cell filled with a culture of the bacillus pyocyaneus. At the end of a few hours the cell contained a large number of leucocytes; but it was not the same if after the introduction of the Hess cell an intravenous injection of 10 c.c. of a sterile culture of the bacillus pyocyaneus were made, then the cell contained a very small number of the leucocytes. In many similar experiments made upon the rabbit, guinea-pig, and dog, with many other bacteria the results have been the same. In another work Bouchard describes the following experiment: He inserted under the skin of rabbits Hess cells filled with a culture of the bacillus of blue pus, leaving some of the animals at liberty, and confining others with a view of producing refrigeration; in the former the cells were quickly filled with leucocytes, while this effect was much less marked in the latter. These researches, as well as those of Massart and Bordet, show very clearly that the predisposing causes above mentioned oppose the gathering of the leucocytes at the threatened points; their chemotactic power is thus diminished or taken away.

As to the reason for this loss of power, Bouchard concludes from his first study that the bacterial products exercise a stupefying effect upon the leucocytes; when a sterile culture is introduced into the circulation the white corpuscles are paralyzed, and cannot mass themselves in the neighborhood of the virulent bacteria. It is in this way that the absence of the leucocytes in the Hess cells is to be explained when they are filled with a culture of the bacillus pyocyaneus,

and at the same time 10 c.c. of a sterile culture fluid is injected into the veins. But this theory is open to many objections that rest on experimental evidence, as shown by Massart and Bordet, whose researches were made with the bacillus prodigiosus. Roger showed that the injection of this bacillus made rabbits susceptible to symptomatic anthrax, and Vaillard and Vincent also showed the same thing for tetanus. Two similar experiments by Massart and Bordet showed that the injection of the bacillus prodigiosus facilitates in the rabbit the appearance of pyocyanic disease; they further seemed to show that when bathed in the culture of the bacillus prodigiosus the leucocytes are neither stupefied nor paralyzed (Bouchard), but retain complete their irritability and their motility.

Finally, as the result of their work upon this general subject of the chemotactic power of the leucocytes, Massart and Bordet come to the conclusion that the increase of the susceptibility of the body to the infectious diseases may be influenced by various causes, of which the following are some: 1. The leucocytes are "bathed" in the fluids charged with the products secreted either by the bacteria, or by the altered cells; these products attract the phagocytes, retain them in the tissues, and prevent their migration towards the threatened points, while under normal conditions the phagocytes move in the direction of these points by virtue of their chemotactic properties. 2. The leucocytes are repulsed from the invaded regions by pathogenic bacteria, because of products secreted by them that have a negative chemotactic action. 3. Anæsthetics facilitate or aggravate infection by suppressing the irritability of the phagocytes.

Charrin and Duclaux, speaking of bacterial toxic products acting as secondary agents in the production of infectious diseases, explain this as follows: To conquer the resistance of the body assistance is often called in by the bacteria; and among these aids are often the toxic substances, and this notion has been confirmed by experimentation. At the same time the authors seem to have confined themselves to the simple registration of facts without attempting to explain their deeper meaning. Nevertheless Roger and Monti have shown that under these circumstances the bacterial poisons act much more by an attack upon the general system than by one upon the locality of development of the bacteria. Bouchard also attempted to show that the action of these poisons was especially upon the phagocytic activity.

Since every day made more manifest the influence of various intoxications upon the bacterial effect, it seemed to be interesting and of importance to elucidate the mechanism of this influence. The experiments consisted in inoculating cultures of slightly pathogenic bacteria or attenuated cultures in animals, and at the same time in

other localities injecting poisons of various kinds, such as weak lactic acid, acetate of lead, bichloride of mercury, tuberculin, mallein, and pyocyanic toxins, thus utilizing organic and inorganic poisons. In the immense majority of cases the tissues of an animal thus poisoned showed a far larger number of colonies than those of one inoculated in the same way but not injected with the poison. The facts demonstrated then that the poisoning influenced the quantity of the bacteria present, and further experiments were made to show whether or no the quality was affected as well. The results seemed to show that the poisons used tended to lessen the quality of the virus by their antiseptic qualities. Also that in the inoculated animals the bacteria, while they developed more freely if the poisons were also introduced, did not at the same time acquire any increase of virulence. Is this action of the virus a direct one, or is it due to an alteration of the soil upon which the bacteria grow? The absence of an increase of quality (virulence) tends to show that there is a disturbance of the economy in which this virus develops, but as always in such a matter experimentation only can furnish the solution. It is therefore logical to seek the explanation of this excess of quantity in an examination of the possible changes that may have occurred in the animal body under the influence of the introduction of the toxic elements. The conclusions to be drawn from the experiments are that the poison acts upon the means of defence of the body against the action of the bacteria, and that the particular defensive means that is affected is the phagocytosis rather than the bactericidal condition. Thus, if the bacterial destruction due to this phagocytic power does not occur in the animal experimented upon, while it does occur in a control animal, it is clear that the bacteria must soon appear much more numerous in the given animal than in the control; in other words, there is some marked disturbance of the organism, which reacts indirectly upon the virus. These experiments generalize the rôle of poisons in the genesis of infection; they demonstrate that a virus (bacterium) by reason of the toxic antiphagocytic action, gains in amount without increasing in virulence. It is, in the last analysis, this increase in number of the bacteria that makes the virus more remarkable, whether it really depends more upon its quantity or its quality.

Concerning the bacterial products favoring the development of infection, Roger says that among the substances secreted by the bacteria are some that produce intoxications and others that produce vaccinations, and experiments that he has made seem to demonstrate that they may also favor the development of certain pathogenic agents, at least in symptomatic anthrax. It is known, he says, that this bacillus may be injected into rabbits without result, but he has

found that when it is associated with some other, as the staphylococcus pyogenes aureus, the proteus vulgaris, and especially the bacillus prodigiosus, injections of the two together give the most rapidly fatal results. This fact is all the more curious because the bacillus prodigiosus is not a pathogenic bacterium and can be injected into rabbits without any fatal results even in enormous quantities, so that we have the result that two bacteria that are harmless by themselves produce grave results when injected together.

In attempting to explain the mechanism of the action of the bacillus prodigiosus in favoring the development of symptomatic anthrax, Roger recognized that it acted by means of its secreted products; for the anthrax developed as well when there was injected at the same time with this virus a sterilized culture of the bacillus prodigiosus, as when a watery extract of the cultures was used, that is to say, the matters that were insoluble in alcohol. It was entirely natural to suppose that these compounds exercised a local hurtful influence, and favored the development of the infection by an alteration of the muscle. But such an hypothesis does not conform to the facts, for the symptomatic anthrax develops as well when the anthrax cultures are injected in one place, and the prodigiosus at another some distance removed, and the results are even more sure and rapid when the two injections are made at separate points than when they are made together. But the most striking results are obtained when the anthrax virus is inoculated in a muscle and the prodigiosus in a vein; whether one has used a living culture, a sterilized one, or watery extracts, the animal dies within twenty-four hours with an enormous anthracoid tumor. This result is obtained with minute doses of the prodigiosus, so much so that while it requires a dose of at least 1 c.c. of a culture of the prodigiosus to produce any result when injected at the same point with the bacillus of symptomatic anthrax, it needs only a single drop of the same culture to produce the same result when introduced into a vein; this malady develops equally well when there is injected into the vein a single drop of the watery extract of the bacillus prodigiosus, while if the injection be made in the muscle, there must be used at least 2 c.c. of the watery extract.

These experiments seem to demonstrate that the prodigiosus favors the anthracoid development by secreting toxic substances that once introduced into the circulation alter the condition of the animal so as to render it more susceptible to action of the anthrax material.

What the prodigiosus can do, the symptomatic anthrax bacillus can do for itself. If the serous fluid of an animal dead of anthrax be collected and filtered through porcelain it can be injected into animals in doses of 4 or 5 c.c. per kilogram without producing any appreciable

results, but if 1 or 1.5 c.c. be injected, and at the same time a dose of the anthrax culture be given, the animal will die in a very short time with an enormous anthracoid tumor. These results seem to be analogous to those obtained with the injection of sterilized cultures of the prodigiosus with the anthrax. The analogy goes even further; in both cases the morbid condition produced by the bacterial products appears to be only of short duration, and if twenty-four hours be allowed to elapse before the anthrax material is injected the animal is found to have again become refractory.

The action of the anthrax serum raises a curious question: by the work of Roux, we know that this fluid possesses an immunizing power, so that it would seem sometimes to favor, and sometimes to retard infection. But the contradiction is only apparent; the immunity produced by vaccine does not exist immediately after the introduction of the vaccine, but makes its appearance only at a varying interval after its injection; while on the other hand the predisposition created by the soluble material is fleeting and does not last for more than twenty-four hours. So that one of two hypotheses must be assumed, namely, either the anthrax serum contains a number of substances both chemically and physiologically distinct, and the action of the vaccine does not become manifest until after the elimination of the toxic substances; or, artificial immunity being due to an alteration in the nutrition of the cells of the organism (Bouchard), the vaccine is able to bring on troubles that diminish the resistance of the animal.

The production by the anthrax bacillus of elements that favor its development explains a result obtained by Roger in the course of his researches. The rabbit, that resists so successfully the injection of the anthrax bacillus in its muscular tissue, yields very readily to an inoculation in the anterior chamber of the eye; so that if an injection be made at the same time in the eye and the muscle of the abdomen there appears at this latter point an enormous tumor of anthracoid material; thus one bacterial point may favor the development of another at a distance from the primary lesion. In the actual case the symptomatic anthrax would not have been developed in the abdomen had not the inoculation been also made in the eye; the products that were secreted at this point, having been absorbed, destroyed the immunity of the rabbit, precisely as if the soluble products were injected directly into the vein.

The facts here reported seem to justify the conclusion that among the bacterial products there are some that diminish the resistance of the animal to infectious diseases; sometimes it is a bacterium entirely harmless under ordinary conditions that elaborates some soluble material that places the animal in a susceptible condition, unable to

struggle against the infectious agents, sometimes it is the bacterium itself that secretes substances that favor its own development.

The Local Lesion.

Bouchard's theory of the part played by the local lesion and its mechanism in infectious diseases is, at least, interesting. He had remarked for a long time that the greater the susceptibility the less the local lesion, but has taken care to add that the local lesion reinforces the immunity and diminishes the severity of the general disease. The two formulas do not conflict, and the one is not entirely contained in the other. He selects from facts of pathology examples of these two laws. Man is more refractory to anthrax than the rabbit; inoculation of the anthrax bacillus in man produces malignant pustule, a local lesion that is not often generalized; the same bacillus inoculated in rabbits produces a general infection, or at least one that is only very rarely and slightly localized. Charrin has demonstrated that the guinea-pig is less susceptible than is the rabbit to the bacillus pyocyaneus, and he has demonstrated that the subcutaneous inoculation of the bacillus pyocyaneus, which usually produces in the rabbit a general infection without any local lesion, results in the guinea-pig in a nodule limited to the point of inoculation, which ulcerates, undergoes molecular necrosis, is discharged, and cicatrizes slowly, without in the vast majority of cases producing anything like a general infection.

The normal resistance, the immunity as it is called, therefore favors the development of a local lesion. An absolute immunity prevents the development of any lesion, either local or general. An entire absence of immunity results in a general infection, very often without any local lesion at all. A relative immunity imposes as a rule the production of a local lesion that ordinarily is not followed by a general infection.

On the other hand, the appearance of a local lesion at the point of inoculation produces or reinforces the immunity and diminishes the severity of the general infection as well. It has been known for a long time that inoculated variola gives rise, some days after the appearance of the primary vesicles, to a general infection that is much less severe than ordinary variola, where the infection has taken place by the arrest of the infectious element by the lungs, infinitely less severe than variola in the fœtus, where the general infection takes place through the blood. Acquired syphilis as contrasted with congenital syphilis is also an example of this, and many experimental infectious diseases might also be quoted. If the local lesion pro-

duced a relative immunity, it might be supposed that Bouchard had made an error of appreciation in the first category where it was said that the relative immunity produced the appearance of the local lesion. It might be said that if these animals appear to be refractory, it is because they are able to make a local lesion, and that this local lesion, circumscribing the disease, prevents it from becoming general. Charrin submitted to the Academy certain experiments that appeared to demonstrate that this interpretation was erroneous. He had said that the subcutaneous inoculation of the bacillus pyocyaneus in the guinea-pig produces, at the point of inoculation, a voluminous tumor, that ulcerates and discharges slowly, and that nothing of the sort is to be seen under similar circumstances in the case of the rabbit. He attributed this difference to the greater resistance of the guinea-pig to its natural immunity. He showed also that, if in the first place an immunity is produced in the rabbit, the same local lesion without general infection appears as in the guinea-pig upon inoculation with the bacillus pyocyaneus.

Charrin has shown that the rabbit can be immunized in varying degrees, either by injecting successively under the skin small doses of the bacillus pyocyaneus, by introducing into the veins small doses of the same culture, or by introducing under the skin or in the veins the cultures from which all the bacteria have been removed either by heat or by filtration. Bouchard has demonstrated that the same immunity can be established by the injection, either subcutaneously or intravenously, of the urine of animals affected with the pyocyanic disease. If in such animals there be injected into the veins a quantity of a virulent culture of this bacillus (sufficient to kill in twenty-four hours a fresh rabbit), it will be seen that, in accordance with the length to which the immunizing has been pushed, there will be produced either no result whatever, or else a chronic malady from which the animal will recover. If a culture (virulent) that in fresh animals will not produce any local disturbance be injected into these animals, there will be seen at the point of inoculation a nodule that ulcerates, discharges slowly, and cicatrizes in a few weeks, similar to that which appears in the non-immunized guinea-pig. In this case it is not the local lesion that has produced the immunity; this preëxisted, and it is because of the presence of the immunity that the local lesion has appeared.

In this discussion of the causes of the production of the local lesion, it is certain that account must be taken not alone of the variations of the immunity, but also of the variations in the virulence of the bacteria, and of the number as well. The greater the virulence or the number of the bacilli the greater the chances of general infec-

tion. In a general way, if the immunity is nothing, or if the virulence is excessive, the local lesion is absent, the infection is as a rule general; if the immunity is absolute or the virulence is nothing, the local lesion may not be apparent, but the general infection is also absent; if the immunity is relative or if the virulence is moderate, there is a great chance that there will be produced a local lesion; but if this local lesion does appear, the general infection will not occur; it will appear, however, if the local lesion does not.

Bouchard's experiments permitted him to study the mechanism of the production of the local lesion, and of the protection that it exerts upon the remainder of the organism. These experiments were made, with the assistance of Charrin, with the bacillus pyocyaneus, and gave results very similar to those obtained by Metchnikoff with other bacteria. In two series of rabbits, one healthy the other immunized for varying periods, even for two months, there was injected at the same time the same quantity of a culture of the bacillus pyocyaneus; in some also there were inserted, instead of the inoculation, some of Hess's capillary cells, previously sterilized, and freely communicating with the cellular tissue. At regular intervals, a little of the fluid that collected at the site of the introduction of the cells was taken from the animals of the two series. It was determined that the swelling, very much greater in the immunized animals than in those untouched, was made up of a collection of leucocytes that appeared in both series of animals, but was very slight in the non-immunized animals, very marked in those immunized; and among them the diapedesis went on gradually increasing, while it remained practically stationary in the non-immunized animals. It is an under-statement that at the end of four hours the proportion of leucocytes was one in the non-immunized to one hundred in the immunized. The difference between the two series of animals was not less as regards diapedesis than as regards phagocytosis. In the non-immunized, it is unusual to find bacilli in the interior of the leucocytes; among the immunized, the bacilli were to be found in the migratory cells after the fourth hour. At the end of six hours and a half practically all of the cells (leucocytes) contained them; the bacilli were then very sharply outlined, possessed all their characteristics, and were more or less numerous in every cell—as many as thirty being found in one cell. It does not appear that phagocytosis is seen in such a marked fashion in any other disease. Little by little the bacilli alter in appearance, become deformed, broken up, and dissolve into granules. Sixteen hours after the inoculation these modifications are almost entirely completed, and at the end of twenty-four hours it is with difficulty that the bacteria are made out at all, the digestion is completed.

The number of free bacilli varies remarkably, according as one is examining the immunized or the non-immunized animals. The number that is the same at the time of the inoculation gradually increases in the non-immunized animals; it seems to remain stationary in the immunized animals, and at the end of the fourth hour it diminishes very rapidly. At the end of six and a half hours, while the bacteria are crowded in the serous fluid of the non-immunized, there can be made out only four or five to the microscopic field in the immunized. In the latter, after twenty-four and a half hours, it was possible to find only two free bacilli in four preparations. The fact is to be insisted upon that, while at the end of the fourth hour the phagocytosis has but just become manifest, the difference is already enormous; and this leads Bouchard to surmise that before any cellular intervention whatever the bacilli find conditions in the immunized that are entirely unfavorable to their growth, and which do not exist in non-immunized or susceptible animals; but he does not know whether this unfavorable influence prepares or makes possible the phagocytosis. In any case the bacilli are not killed before the phagocytosis, they remain equally motile among immunized and non-immunized animals. These experiments make it possible to admit that in the infectious diseases, in the pyocyanic disease at least, the animal can conquer the pathogenic bacterium because of having at the start a certain power of resistance, and that this resistance—relative, natural, or acquired immunity—acts by multiple procedures, or results from diverse acts: (1) in animals with a relative immunity the fluids are a medium unfavorable for the development of the bacteria; (2) in such an animal the diapedesis of the leucocytes occurs in the zone first invaded with much the greater intensity, so as to produce a primary tumor, a local lesion; (3) in such an animal the leucocytes exuded possess in a very marked degree the power of phagocytosis which is almost absent in the susceptible animal, and by this power the bacteria are destroyed at the site of the local lesion; (4) it is to be added that during their short existence in the local lesion the bacteria have continued to secrete soluble immunizing material which, when absorbed, reacts upon the general system in a way to increase still more its resistance.

In this connection, Bouchard's theory of infection, cure, and immunity is of interest. He has been able to deduce from experimental facts already communicated to the French Academy a new system of infection and immunity. If the infectious agent upon inoculation enters an animal which furnishes a very bactericidal medium it does not develop, and no disease makes its appearance; if the living animal furnishes a favorable medium, the bacterium develops immedi-

ately; if the medium is moderately bactericidal, there occurs in the life of the bacterium a period of degeneration. For a very short time, some quarter of an hour or so, its multiplication is suspended, but it still lives and by means of its diastases it adapts the material of the tissue in which it may be to its needs; after a time its hindered development reappears. Whether the development has been immediate or has been preceded by a period of quiescence, the malady commences. At the same time as it develops, it secretes in a greater or less amount chemical substances, of which some act upon the nervous system, producing changes of the circulation or of the temperature, manifested by cephalalgia, delirium, coma, convulsions, etc.; others influence all the cells of the body, change their nutritive type, and by their intervention so modify the chemical composition of the fluids of the body that they may become bactericidal. This last effect is slow in making its appearance, but it is durable. The toxic substances acting upon the nervous system are more rapid in their action, but their results are much more fleeting; in the number of these rapid but fleeting results are to be included the paralysis of the vasodilator central nervous system, which makes impossible the passing out of the white corpuscles from the vessels.

As soon as the number of the bacteria becomes so considerable that their products cannot be neglected, the febrile as well as the toxic symptoms make their appearance; phagocytosis alone can come to the rescue of the threatened body. But phagocytosis is rendered impossible, because at the same time with its other products the bacterium has secreted the material that prevents diapedesis. Therefore in a medium that is already favorable to its development and protected against the most important of the cellular reactions, it continues to grow and to secrete its products freely; intoxication increases, the disease becomes aggravated, and death occurs during this period. But during this time the materials that change the nutrition of the cells were being secreted also, although their more gentle action was not yet manifest. At some moment they become sufficiently powerful so to act upon the cells that their nutritive type is changed (modified), and the fluids are in consequence changed chemically. The bactericidal condition is a possible effect of this chemical change. It appears late; but from the time that it exists the life of the bacterium is influenced, its growth either becomes slower or is arrested, and its secretions are suspended. The material that opposes the diapedesis in particular no longer paralyzes the vasodilator centres. Then the white corpuscles pass out of the vessels, and phagocytosis finally destroys the bacteria already weakened by the bactericidal condition; this is *cure*.

Cure is the first manifestation of acquired immunity. The bactericidal condition produced by the passing impregnation of the cells brought in contact with the immunizing elements persists for a long time after the elimination of these elements. If, in the immunized, this bactericidal condition is very pronounced, the bacterium that produced the first attack cannot develop when introduced in a second inoculation; there does not occur either a general or a local infection, the immunity is absolute. If the bactericidal condition is less pronounced it does not destroy the life of the bacterium, but attenuates it and lessens the activity of its secretions; one of them in particular becomes incapable of paralyzing, as before, the vasodilator system, diapedesis is not prevented, and phagocytosis arrests and ends the infection in its original site. The local lesion has been made possible, and it prevents the appearance of the general infection.

Natural immunity does not depend upon the bactericidal condition; it results from the greater resistance that, in certain species of animals, the vasodilator system opposes to the paralyzing materials. The proof is that, if there be injected into these animals certain bacteria that ordinarily start up diapedesis and are pathogenic to other animals, this diapedesis is not manifest if there be injected at the same time with the virus that they resist a strong dose of the material that prevents diapedesis. It can be determined then that diapedesis, and by consequence phagocytosis, is not produced; it can further be seen that the general infection does occur

Racial Temperature.

Racial temperature has been shown to have much influence upon the susceptibility to specific infectious diseases. Many observers have investigated the subject, Pasteur among the first, with anthrax in frogs. Wagner studied the action of anthrax infection in normal chickens, as well as in those artificially cooled (by water and antipyretics) and narcotized. The inoculations were made with anthrax bacilli, as well as spores in the anterior chamber, under the skin, and in the blood. As a preliminary research, a number of control cultures were made in blood serum, defibrinated blood, and in the aqueous humor of chickens, which showed that these fluids were not inimical to the growth of the anthrax bacillus, for it developed well in them, and also showed undiminished virulence upon inoculation in rabbits and guinea-pigs. So that the cause of the immunity of healthy chickens to anthrax is not to be found in the fact that the fluids are not favorable to the growth of the bacilli. Wherein it is to be found is shown by the first series of experiments (infection of

healthy birds). The injected bacteria grow exceedingly well for the first day at the point of inoculation; on the second day begins a phagocytosis, which in most cases advances so rapidly that on the third day it is not possible to make out any bacteria at all, they have all been eliminated. The experiments with injections in the blood gave similar results, the bacteria being removed from the organism by phagocytosis. The temperature of the inoculated animals rose a degree to a degree and a half, remained at this range for a day, and returned to the normal at the same time that all the bacilli disappeared. Birds that at the same time were cooled by placing the lower half of their body in water at 25° C., died with typical anthrax symptoms—phagocytosis was reduced to a minimum. The control animals that were put in the cooling apparatus showed no ill effects from the cooling.

Out of eleven animals in which the cooling was effected by the administration of antipyrin, six were attacked with the disease; of these five died, and the other recovered. This result was to be explained by the fact that the antipyrin reduced the temperature for only an hour, and so the immunity was suspended for but a short time.

This observation showed that the diminution of the immunity was due to the diminution of the phagocytic activity, and also suggested the attempt to diminish the immunity by narcotizing the leucocytes without affecting the body temperature. Out of eight chickens inoculated with anthrax, after being dosed with chloral hydrate, one died (after about sixty hours); of the others, three died from the chloral hydrate, and the remaining four lived. In these also the local reaction (œdema) was well marked, but it disappeared later. The weak action of the chloral hydrate upon the resistance of chickens to anthrax is to be explained by the fact of the paralyzing effect of the drug upon the nervous system.

Centanni, in particular, has given attention to infectious fever, with especial reference to the latest knowledge upon the subject. The research divides itself into three parts: (1) On the agents that bring on the fever; (2) on the mechanism of its working in the organism; (3) on the therapeutic questions involved in the handling of the fever. The conclusions of his work are summed up as follows: 1. The production of the bacterial fevers is carried on by a general intoxication with a poison (pyrotoxina bacterica) which has its origin in the interior of the bacterial cells themselves, and differs in its properties from the as yet better known bacterial poisons (ptomaïns, enzymes, toxalbumins). 2. This poison is widely distributed and common to all bacteria, so that it is found in non-pathogenic, as well as in pathogenic varieties, and always with the same properties.

For the production of the fever poison there were employed especially fluid culture media, and cultures a week old. The medium should contain no peptone; the author calls the product *pyrotoxina bacterica*. The cultures were extracted for three hours at a temperature of 60° C., and then for as long a time at boiling temperature. The bacteria were filtered off by a Chamberland filter, and the filtrate was moistened. The impurities (remains of the culture medium and soluble products of the bacteria) were dissolved in alcohol and removed. The precipitate and the fever poison were dissolved in distilled water, the fluid was placed in a dialyzer of parchment paper in a glass (filled with distilled water) and protected by chloroform or thymol from putrefactive changes.

The water first passing through the dialyzer was rejected, being rich in salts and coloring matter; that coming after was concentrated after two or three days. This concentrated solution of the active and albuminoid free principles was treated with alcohol, and the resulting precipitate was washed later with water and again precipitated with alcohol. The preparation was isolated by pouring off the alcohol and then drying over sulphuric acid. The body is an amorphous powder soluble in neutral or faintly acid or alkaline water and in alcohol up to ninety per cent., but precipitated by stronger alcohol, and insoluble in chloroform or ether.

As culture media, urine, the usual bouillon, or meat extracts with sugar or glycerin are useful. The pyrotoxin gives no reaction with Millon or the biuret test, as does xanthoproteic acid, and no precipitate follows with ferrocyanide of potassium and acetic acid.

All albuminoids, to which the toxic products belong, are excluded —the toxipeptones, toxalbuminoses, proteins, and alkalialbumins of Buchner, as well as the ptomaïns and enzymes. The coagulable albuminoids are shut off by the heating. The pyrotoxin therefore is a body that belongs in no one of the known categories of bacterial products. Inoculated with this pyrotoxin rabbits showed all the phenomena of bacterial fever. The changes of temperature manifested themselves first by a fall of a degree and a half, and then there occurred, in about two hours after the injection, a rise to from 39°–41.5° C. A further result was the extreme emaciation. The digestive apparatus was also affected, as evidenced by the occurrence of diarrhœa and loss of appetite. Nor were the other clinical symptoms, quickening of the pulse and respiration and diminished sensibility, lacking.

Pyrotoxin acts usually like a bacterial centre. In capillary tubes under the skin it produces a positive chemotaxis; injected in solu-

tion, it produces no centre of attraction for the leucocytes before its rapid absorption, but only a gelatinous œdema.

The bacterial fever can be produced not alone by the cultures or the products of the cultures of the pathogenic bacteria, but by the non-pathogenic bacteria as well; the pyrotoxic power of the various bacteria is not in proportion to their pathogenic power. A marked difference in favor of the pathogenic bacteria is seen only in the fact that these can be injected in small quantities and are then quickly developed and distributed, while the non-pathogenic bacteria act only in large doses and at the point of inoculation. The different bacteria seem to contain the pyrotoxina bacterica in about equal amounts, volume for volume.

Notable changes in the amount of poison produced by a special variety of bacterium occur under varying circumstances; meat infusion gives a larger amount than an agar culture in the same degree of concentration.

A notable difference also exists between spore and non-spore-producing cultures. The toxin remains entirely in the former, so that it appears as if the toxin-producing power is either destroyed in the spore-producing stage or else that the poison is shut up in the spores and cannot be extracted. Of the two constituent parts of the bacteria, linin and chromatin, the latter is the first diminished; when the pyrotoxin is diffused or distributed in old cultures or in the organism, it seems as if the chromatin goes to make up a part of it. Other substances may be produced than the pyrotoxin, but probably only in special cases. Most of the so-called bacterial poisons are brought back to the pyrotoxin. Because of its universality it must be looked upon as the head of the bacterial poisons, which, because of their occurrence only at times, must be considered simply as accidental, secondary, or, better, "specific" poisons.

If it were a fact that this pyrotoxin is universal for all bacteria, it would be superfluous to seek for a special immunizing substance for each individual bacterium, for in that case if an antitoxin for the fever of one bacterium were found, an antitoxin against the fevers of all bacteria would have been found.

In the enthusiastic search for specific curative agents, it is to be feared that the study of the influences which conduce to spontaneous recovery from the acute infectious diseases has been in a measure neglected. The importance of a correct knowledge of the way in which spontaneous cure is effected cannot be overestimated, since any rational cure by artificial means to be most effective must follow in the same line. A correct understanding then of the natural history, so to speak, of the infectious diseases is of the greatest importance.

Fever.

Of all the symptoms of the acute infectious diseases fever is the most constant, yet of the manner of its production, and of its influence upon the course of these diseases, we are almost wholly ignorant. At the present time, the immediate practical importance of this question is very great, since so large a part of the treatment of these diseases consists in combating the fever which is so constantly present. The fallacy of such treatment is apparent, if in fever we have one of the salutary influences which bring about the natural recovery from these diseases.

In this connection, the recent experiments of Loewy and Richter are of exceptional interest. By making use of the Sachs-Aronson method of puncture of the corpus striatum they were able to induce in rabbits a fever of more or less intensity and of the continued remittent type. When inoculated with virulent cultures of the germs of diphtheria, chicken cholera, swine plague, and pneumonia, these animals were much less affected than others similarly inoculated in which fever had not been induced. In the experiments in which one hundred times the fatal dose of chicken cholera, diphtheria, and pneumonia were used, there was a distinctly slower progress of the disease in the febrile animals, and in these cases in which only two or three times the fatal dose was used the febrile animals recovered. In cases in which the swine plague bacillus was inoculated into the ear vein of rabbits, the local process developed more rapidly in the febrile animals than in the control animals, but notwithstanding this fact many of them recovered, while the control animals all died. These results are the more significant since it is fair to suppose that by the operation necessary to the puncture of the corpus striatum the predisposition of the animals so treated must have been increased.

In their investigation of the effect of an increased number of leucocytes upon the course of various infectious diseases, Loewy and Richter induced artificial leucocytosis by means of pilocarpine, spermin, and various albumoses. Animals so treated were resistant to three and four times the fatal dose of the pneumococcus, there being only a slight rise of temperature and insignificant symptoms in the cases in which the leucocytosis existed at the time of the inoculation. When the pneumococcus infection was allowed to progress for twenty-four hours before the induction of leucocytosis there was a greater mortality, though even then benefit seemed to result from its induction.

In conclusion, the authors express their belief that fever and leucocytosis should be regarded as of assistance to the body in combating

the effects of infection, and they suggest that therapeutic benefit may be derived rather from the use of means tending to increase these conditions than from those antagonizing them.

Protective Function of the Spleen.

The function of the spleen in infectious diseases has been a matter of much interest. Bardach, in his first attempts to settle this question, worked with dogs, and found that after intravenous injection of anthrax bacilli fifteen out of twenty-five that had had the spleen removed died of the disease, and only five out of twenty-five not operated upon. The experiments of Kourloff that had entirely different results do not seem to be admissible because rabbits were used for the experiments, and they are very susceptible to anthrax anyway, and the delay of the time of death is not a proper test from which to draw any conclusions.

Undertaking a new series of investigations, rabbits, which withstand the extirpation of the spleen very well, were used, but the injections were made with *attenuated* cultures which were injected into the vein of the ear. Thirty-five such injections in healthy rabbits produced no result except a very slight fever; but of thirty-five rabbits with extirpated spleens (operated upon from one to three months before), twenty-six died of anthrax.

These striking results can lead only to the conclusion that the spleen is the most important of the organs that play any part in the control of the infectious diseases in the living body. This latter conclusion is, however, not absolute, but only probable, for there may be some alteration of the fluids of the body due to the absence of the spleen, and this alteration of the fluids may lead to an increased susceptibility to the infectious diseases.

A curious observation is that of Dastre and Loye, who have seen that by intravenous injections of salt solution one could produce an apparent washing out of the blood and tissues of the animals experimented upon; the fluid passes into the blood, then into the tissues, and then back again into the blood. They, therefore, went on to see if such a washing of the blood would not take away some of the soluble and toxic material present in infectious diseases, and perhaps cause its excretion by the kidneys. For this purpose dogs and rabbits were injected with cultures of the anthrax, glanders, and pyocyaneus bacilli, and sometimes an intoxication was produced with the toxic products of the diphtheria bacillus, and the growth of the morbid symptoms was watched. In a second group of animals, a short time after such infection, the intravenous injection of salt solution

was performed. The observation of these two groups of animals showed, however, that those treated in the latter way were more severely affected, and died much more quickly than the others that were let alone.

This result may be explained in one of two ways, either that the injection of the salt solution lessened the resistance of the animal, so that it was more susceptible to an infection or an intoxication; or that the salt solution, by diluting the toxic materials, enabled them to be carried more rapidly and more thoroughly into the tissues than under ordinary conditions.

De Ruyter found in a large number of cases of the infectious diseases that the absorption bands of the blood-coloring matter were unchanged, and in malignant œdema as well. But he also found that, if he left the blood standing for a day, between the oxyhæmoglobin bands there appeared a third very closely resembling the methæmoglobin bands but varying somewhat from the borders of this; this change he found in three cases of severe sepsis after diphtheria.

Changes of this sort in the blood in infectious diseases should be the subject of further investigation, and doubtless will be in connection with the studies of the changes in the formed elements of the blood.

Insects as Carriers of Infection.

That insects may be the means of carrying infection has long been suspected. Since the study of the bacteria has been so carefully pursued, evidence to support this idea has constantly accumulated. As regards flies, a writer in the Boston *Medical and Surgical Journal* says that certain experiments that have recently been made seem to offer an explanation of the sporadic cases of cholera occurring, in New York especially, but in other places as well, in spite of the most careful quarantine. It has occurred to many people that the common insects might be the carriers of the infectious material to points at a distance from the centre of infection, and the experiments of Maddox, Simmonds, and Sawtchenko furnish the first evidence on this point. The first two fed flies with cholera spirilla, and obtained cultures of the bacterium from the insects so fed. Sawtchenko proved that the bacteria are not only taken into the fly and pass through its body without any loss of their active properties, but also that in all probability they multiply during their sojourn there. Very numerous colonies were obtained as late as the third day after feeding. The species which took most naturally to this diet was the common meat-fly of the markets. Very little is known as to how far flies travel, or how much they move about from place to place. In a letter

from Professor Packard, to whom the subject was referred, it is stated: "The rate of speed of Musca domestica is 5.35 metres a second according to the observer. This would give about a mile in five or six minutes, or about ten miles an hour. Flesh-flies are a little more vigorous. Any of the flies could scent their food or decaying bodies for several miles, and might fly over twenty or thirty miles a day, especially if aided by a wind." From what has been said, it seems as if the possibility of the carrying of infection by flies had been proved. The history of the outbreak of cholera in New York is given by H. M. Biggs in the *American Journal of the Medical Sciences* for January, 1893. "On August 31st, the *Moravia*, and on September 3d, the *Rugia* and the *Normannia* arrived, all with cholera on board. The first person affected in New York City was taken ill September 5th, five days after the disease was in the harbor, and died on September 7th. During the four weeks following, six other cases occurred in New York and one case in New Brunswick (N. J.), in which the cholera bacillus was found. Three others were regarded as such, from the clinical symptoms, making eleven, and all among the poorer classes. Each case was carefully examined and investigated by the Board of Health, but it was impossible to find any satisfactory way to account for the infection. The cases occurred in widely separated parts of the city; and in no instance was there the slightest suspicion of association. There was a striking association of the persons affected in their occupation with the food trades, especially animal foods. The biological examination showed the bacillus to be in every way identical with that from the cases on the ships." The facts in the above record that have a bearing on the probability of the cases having originated through the agency of flies, are (1) the occurrence among a class of people who would probably be less careful of the contamination of their persons and food from such a source; (2) the association with the meat trades, which would tend to draw the kind of flies most ready to take up the cholera spirillum; (3) the irregular distribution throughout the city, the farthest case being within the limits of an easy day's journey for a fly. The outbreak is further interesting as the ordinary channels of infection, personal contact and contamination of the water-supply or ground water, can with certainty be excluded, thus narrowing down the problem to one of atmospheric transmission. If the wind is taken as the agent (aside from the fact that the prevailing wind was from the west through the north to the northeast from August 31st to September 5th), it is incredible that enough bacilli could have been carried to the distance where the first case occurred to do any harm if they could have withstood the desiccation during the transit. On the

other hand, a single fly can contain enough active bacilli after three days to produce a fatal case, and his association with man and his food renders such a mode of infection very possible.

It is readily acknowledged that many links in the chain of absolute proof are wanting; but now that attention has been drawn to the subject it is felt that the future may throw more light upon it. For the present, the theory offers a rational explanation for such cases as occurred in New York in September, 1892, and gives something else of a tangible nature for the consideration of preventive medicine.

Yersin has found the bacillus of bubonic plague in flies infesting his laboratory, and many workers with the bacteria have upon occasion seen these insects sowing colonies upon plate cultures where they walk, when accidentally shut up in the double dishes. Many isolated cases of the probable transportation of infectious material by insects may be found in the literature.

Book infection has also attracted attention, and on this subject the Boston *Medical and Surgical Journal* says that in many of the European cities extensive investigations have been made to prove or disprove the infectiousness of books handled by the sick, such as must of necessity frequently occur in large circulating libraries. The editor of the Christiania (Norway) *Sanitary Journal*, in commenting on the subject, remarks that it is the universal pastime of invalids or convalescents to read or look over books, which, if not procurable at home, are brought from some library. Even children are fond of looking at picture-books, and the editor relates the following personal experience: "In 1846 an eight-year-old brother of my wife was taken down with scarlet fever and died. During his illness he frequently amused himself by looking over a large picture-book. This, together with several other of his useful playthings, was packed away in a trunk after he died. Twenty-six years afterwards, in 1872, a sister-in-law of mine journeyed across the channel to England, where I was then residing, and with her came the chest and picture-book. On the second day the chest was opened, and the picture-book presented to my two-year-old son. Within the next two weeks the little fellow was taken down with scarlet fever. The doctors who were called in consultation wondered how the disease was contracted, as there had been no scarlet fever in the town for years. The circumstances of the book were called to mind, and the indications were clearly that the twenty-six-year-old book had retained the poison, and communicated it to the child."

Meat of Tuberculous Animals.—Kastner in his earlier researches came to the conclusion that the meat of tuberculous animals did not contain the bacilli. Steinheil, investigating the same subject

later, found that the flesh of highly tuberculous animals contained many bacilli. The marked difference between these results and Bollinger's was explained by Kastner in a new series of experiments in which he worked with cheesy material, and not with calcified. There were in all twelve experiments made with the flesh of seven different animals; it was fresh, and had apparently undergone no tuberculous change; it was chopped fine, pressed in a meat press, and 2 c.c. of the juice was injected either subcutaneously or intraperitoneally in guinea-pigs. Ten times the results were positive, and the animals upon being killed at the end of two months showed more or less tuberculous changes. The importance of these results lies in the necessity of laying stress upon the anatomical appearances in judging of the danger of the transmission of the infectious material by any given specimen of meat, as to whether there exists a cheesy or a calcified process.

Mixed Infection.

The subject of mixed infections is an important one, but full of perplexing problems. That more than one variety of bacterium is often active in a given process is well known, and the experimental testing of the matter is well illustrated by Fessler, among many others, in a study on mixed infection, which was undertaken because of the assertion of Roger that the pathogenic action of many bacteria (malignant œdema, anthrax) was noticeably increased by the simultaneous injection of cultures of the bacillus prodigiosus. The experiments were carried out as follows: injection of prodigiosus and streptococcus, two times; of streptococcus pyogenes, two times; of prodigiosus, two times; of sterilized prodigiosus, one time; of streptococcus and sterile prodigiosus, two times; of prodigiosus and sterile streptococcus, one time. The results showed that the streptococcus pyogenes produced an erysipelas when injected in the ear of a rabbit, but that this erysipelas became a severe phlegmon with suppuration and tissue destruction upon injection of the prodigiosus with the streptococcus, under which the general condition of the animal suffered very much; while the prodigiosus alone in the rabbit's ear produced a very slight, hardly noticeable, inflammatory reaction and suppuration. The toxic products of the one or the other bacterium, whether injected with the streptococcus or the prodigiosus, produced no influence upon the result. These combined infections appeared to be analogous to the pernicious mixed infections occurring in man.

In Roger's work, alluded to above, in regard to the relationship of bacterial products to the production of disease, it is stated that he injected rabbits and guinea-pigs with living cultures of anthrax bacilli

and sterilized cultures of the bacillus prodigiosus. He obtained in these experiments very varying results. In the rabbits that were inoculated with the two cultures, the results were much delayed, and sometimes did not occur at all, while the control animals inoculated with anthrax alone died in from two to five days. But exactly the opposite occurred in the inoculation experiments with guinea-pigs; in this case the animals inoculated with the mixture became œdematous, and died very quickly indeed, while the progress of the disease in those injected with anthrax alone was slower. These experiments gave such absolutely opposite results that the observer utters a warning against the application of the interpretation of similar results to man. (A reviewer refers, as an example of this, to the experiments of Rumpf and Fränckel on the healing of typhoid fever by bacterial products.)

From the clinical side, Muhlmann says that, when a mixed infection is apparent by reason of the different complications or aggravations of the symptoms in a series of diseases, the nature of the mixed infection may be of importance to the practitioner. Many workers have busied themselves with the action of known bacteria upon others in the way of attenuating their action; for example, Fehleisen with the streptococcus of erysipelas on tuberculosis (lupus); Cantani with bacterium termo on pulmonary tuberculosis; Emmerich and Pawlowsky with the streptococcus of erysipelas on anthrax; Pawlowsky and B. Friedländer with the bacillus prodigiosus and staphylococcus aureus on anthrax; Bouchard and Guignard, Freudenreich, Woodhead and Wood, Charrin, and Blagoveshchensky with the bacillus pyocyaneus on anthrax; Buchner with the bacillus of Friedländer on the same. The enhancing action of one form of bacterium on another has been especially studied during the last year or so. Roger succeeded in producing a pathogenic action with two non-pathogenic bacteria, bacillus prodigiosus, and an anaërobic bacillus. Monti and Klein have brought back the pathogenic property of an attenuated micrococcus by the addition of the proteus. Klein has also increased the action of the bacillus of diphtheria by the addition of bacillus pyocyaneus. Roux and Yersin, and von Schreider have also increased the virulence of the diphtheria bacillus by the addition of streptococci. Finally, Trombetta, as well as Grawitz, de Bary and Stern, and Hirschler, have succeeded in making attenuated bacteria go back to their original virulence by the addition of other varieties.

Trombetta's attention was first called to the importance of knowing the nature of a mixed infection in cases of tuberculosis, typhoid fever, diphtheria, etc., in the hospital at Odessa, and he undertook to study the nature of various infections. His investigations were car-

ried on with two bacteria, Fränkel's diplococcus of pneumonia and the anthrax bacillus, which, mixed in various proportions and in varying degrees of attenuation, were injected subcutaneously in mice and rabbits. The diplococcus of pneumonia is more pathogenic for rabbits than for mice, as is known; the anthrax bacillus is the reverse. The diplococcus used by him was at the start very virulent, 2 (?) c.c. of a bouillon culture would kill a rabbit within twenty-four hours; but the culture was so attenuated by its growth upon the usual nutrient media that at the fourth generation, 2 c.c., and at the ninth, 4 c.c. of the bouillon culture would not kill, but only produce an abscess at the point of inoculation. A diplococcus of this sort, that in large doses would not kill the animal, was used in all the following experiments. On the other hand, the anthrax culture that was used was very virulent, and would kill a mouse in twenty-four hours, and 1 c.c. of a bouillon culture killed a control rabbit in three days. Other workers on this subject have been Kruse and Pansini, Nencki, and v. Sieber.

The conclusions of the authors may be summed up as follows: that, as Monti and Klein gave virulence to an attenuated bacterium by the addition of a saprophyte, so they obtained the same result by the mixing of pathogenic bacteria that were either attenuated to the special organism in which they were injected, or towards which the organism was more or less immune. As a matter of course, it became evident, as Klein's experiments made certain, that the amount of the dose administered made a great difference upon the result. It was seen also that a previous withstanding of the virus of the diplococcus pneumoniæ rendered the organism susceptible to a mixed infection, in other words that the immunity, whether great or little, was destroyed.

E. Klein concerned himself with two sorts of experiment in which he first worked upon a double infection. When mice are inoculated at the same time with hog-cholera and chicken-cholera bacteria, the animals die with "swine fever" as quickly as if inoculated with hog-cholera bacilli alone. Only hog-cholera bacilli were found in the blood and the organs. The chicken-cholera bacillus exerted no inhibiting effect upon the disease production or the growth of other bacteria in the same body.

While in these experiments the attempt was made to introduce as nearly as possible the same amounts of the two bacteria at the injections, in a second series of experiments, made with the bacteria of hog erysipelas and of hog cholera, there was introduced a much larger quantity of the hog erysipelas than of the other. When such a mass was injected subcutaneously the mouse died within a day of

hog erysipelas. The bacillus of hog cholera was not found in the blood, although the number of bacilli in such a mixture was sufficient to kill a mouse by itself. In this case then the erysipelas bacillus had overcome the hog-cholera bacillus.

When equal masses of bouillon cultures of these two bacilli were injected, the animal died as quickly as if inoculated with the hog-cholera bacillus alone, and in the blood the erysipelas bacillus was found in very much smaller quantities. Cultures of these two bacilli made upon gelatin, and injected into two mice, produced death with a mixed infection; so that there appears to be no antagonism between the two, although allowed to grow for a long time upon nutrient gelatin.

In another series of observations, the experiments were carried on with a mixture of the erysipelas coccus and the toxic products of the proteus vulgaris. When at the same time an attenuated culture of the streptococcus of erysipelas and a sterile or non-sterile culture of the proteus vulgaris were injected in a rabbit subcutaneously, the animal died in from one to three days of a general infection. Control animals inoculated with the streptococcus alone did not die. The attenuated coccus also regained its original virulence in this way; it was equally so whether the two substances were injected together or separately. Cultures of the proteus vulgaris injected in rabbits had no after-effects. It was also noticed that the local reaction of the streptococcus was restored by the chemical products of the proteus. It is with the erysipelas coccus as with the pneumococcus; the lost virulence may be restored by the toxic products of a common organism like the proteus vulgaris.

The subject of mixed infection is so vast that, as may be readily seen, it cannot be well treated as part of a general article.

Late Results of Infection.

Late results of infection form a field for study, well summarized by Charrin, who says that in experimental pathology we know especially the immediate effects of the infectious diseases, those that are manifest while the bacteria are multiplying and active; but we know much less perfectly the later results of these diseases, those that belong directly to the infection, but which become manifest long after the bacterium has disappeared. The reasons for this are that for the most part the experimental animals are not kept for a long enough time, and that generally the infectious diseases terminate so promptly in death.

It is, however, possible by means of protective procedures so to

treat an animal as to endow it with such resisting powers that the inoculated bacterium shall produce only a modified form of disease that shall at least apparently pass on to complete cure. In the case of the paralyses produced by the inoculation of the bacillus pyocyaneus, if the animal be protected before the intravenous injection, these paralyses (which can be produced as well by the soluble products as by the bacilli themselves) either do not appear at all, or else very late, two, three, or more months after the inoculation. If search be made for the bacilli at this time, they will not be found either by microscopical examination or by culture, although it was easy enough to demonstrate their presence within a few days after the inoculation. An error in technique cannot account for their not being found, for they were present at first unquestionably, and what is left are functional troubles of the nerve cells irritated at some period by the bacterium itself or by its products.

In another experiment Charrin was able to keep a rabbit for eleven months, thanks to previous immunization. During these eleven months the rabbit received three times by intravenous injection doses of the bacillus pyocyaneus sufficient to kill control animals in two or three days. Immediately after the inoculation the bacillus could be found in the urine, but after a short time it disappeared. During the last three months of the animal's life the bacilli could not be found at all, and cultures of the blood and of all the organs remained absolutely sterile. But during the last months the animal suffered from a progressive albuminuria that began at the time of the intravenous injections of the culture, and at the autopsy the kidneys were found sclerotic, granular, and with epithelial alterations and considerable amyloid degeneration, and the left ventricle of the heart was dilated as well. As it is well known that the bacillus pyocyaneus, either by itself or by means of its products, produces nephritis, it is permissible to conclude that this chronic nephritis could be traced directly to the presence of the infectious agent in the blood and urine of the animal; that this infectious agent, the presence of which was established by examination at first, had disappeared, as shown by the cultures, but that the cells injured by it had continued to develop in a pathological and not in a normal way. The bacilli no longer existed, but the cellular alteration continued, as is seen in human infections or intoxications. One can at a definite moment stop the supply of lead or of alcohol, but the progress of the sclerosis cannot by this be arrested. A scarlatina or a diphtheritis is over, but there is seen to follow a nephritis or a paralysis.

Among the changes produced, those described by Thérèse as occurring in the arteries in infectious diseases are interesting. After

the injection of various kinds of bacteria, streptococci, staphylococci, and diphtheria bacilli, the anatomical changes of the various internal organs, especially of the arteries, heart, and kidneys, were studied. The arteries of the latter were of especial interest. There was particularly an interstitial inflammation of varying intensity that entered the vessels from the surrounding connective tissue. There were found, for example, in the hearts of guinea-pigs injected with attenuated diphtheria bacilli the ordinary appearances of acute infectious myocarditis, and in an animal dead on the thirteenth day and in one dead during the third week, when the process had well progressed, there were found appearances that were strikingly like those in man. There was an inflammatory reaction in the adventitia of the medium and large arteries, but there was no change found in the intima; this is an observation of very great interest in connection with that of Landouzy regarding the extreme frequency of infectious endarteritis. The observer considered the inflammation of the adventitia as the first step of arteriosclerosis. That the observed changes were not the result of the direct action of the bacteria themselves, but of their products, was shown by the injection of a filtered culture of a streptococcus, which produced the same changes.

Jawein made a whole series of experiments upon rabbits and guinea-pigs to demonstrate the occurrence and pathogenic action of toxins in the urine of affected animals. For the infective purposes he worked with Fränkel's diplococcus, bacillus pyocyaneus, streptococcus of erysipelas, bacillus of anthrax, vibrio of Asiatic cholera, and bacillus of hog cholera; specimens of the urine of these animals were injected into the abdominal cavities of other animals in order to determine their infectious properties.

The conclusion was very soon reached that all these bacteria appeared quickly in the urine of the infected animals, that pure cultures could be obtained from this fluid, and that the pathogenic powers of these suffered no diminution, since the pure cultures so obtained gave the characteristic results in inoculated animals. That a certain toxin was produced in the urine of animals inoculated was demonstrated in the case of Fränkel's bacillus, the erysipelas streptococcus, the bacillus of anthrax, and the bacillus pyocyaneus, in which the "urine bacteria" were destroyed by chloroform or by an hour's exposure to a temperature of 58° C.; the animals that were inoculated with urine treated in this way very quickly died of the expected cachexia.

In the experiments with the cholera spirillum in guinea-pigs, it was shown that the urine contained no bacteria (of cholera), especially when the injection was by the abdominal cavity, but not a sufficient

quantity of urine was collected in these cases to determine whether or not there was a toxin present. After subcutaneous inoculation of cholera spirilla (in rabbits) the bacteria die very quickly, and do not pass into the urine, and the injection of this urine into the abdominal cavity of other animals demonstrates also that it contains no toxins. The urine of rabbits inoculated with hog cholera bacilli contains a substance that, transferred to other animals (rabbits), produces a high degree of immunity to a fatal dose of these bacilli. That this substance is not the hog-cholera toxin is shown by the absence of the symptoms that are characteristic of hog-cholera-toxin poisoning.

The results show that one does not have to do with specific toxins secreted by the kidneys, but that toxins are observed in the urine only when the urine contains the special bacteria. The question whether the toxin is present in the urine through the vital activity of the bacteria, or whether it is secreted by the kidneys is left open. If there are no bacteria present in the urine, no toxin is present, but there may be present (as in hog cholera) an immunizing substance.

Following a similar line of investigation, Pernice and Pollaci made the repeated observation that, if dogs were inoculated with a known quantity of anthrax bacilli, they remained with all the apparent symptoms of well-being; but if the same quantity of anthrax bacilli was inoculated after an experimental and more or less complete anuria was established, when, during the time that the bacteria existed in the body, the functions of the kidneys were destroyed or limited, then dogs so inoculated presented the symptoms of the disease, and soon died. Death occurred usually in from twenty-four to forty-eight hours after the inoculation, at a time when it is easy to differentiate from death due to uræmic poisoning; the existence of the pathogenic bacteria in the body is of brief duration, for they disappear very quickly.

From such results the conclusion is reached that the activity of the urinary apparatus and of the secretory apparatus in general, preserves the body from infections, and it is possible that it has an influence upon the beginning and ending of the infectious diseases.

External Predisposing Influences.

Various external influences have to do with predisposing to infectious diseases. Charrin and Roger, recognizing the clinical fact that overstrain and fatigue result in a predisposition to the infectious diseases, endeavored to cast some light upon the matter by inoculating large animals with equal amounts of infectious material, and placing some of them in a rotating cylinder for from two to eight

hours. The rotation amounted to about 2,260 metres an hour, and 16 km. (10 miles) in seven hours. Guinea-pigs and rabbits were of no use in the experiments, for after a few moments in the apparatus they collapsed with a rapid rise of temperature. Dogs and cats stood the manipulation better, but the best were white rats which stood the working for the entire day, and were even bright in the morning when the apparatus had been kept working all night. The experiments were made with strong and attenuated anthrax bacilli, and justified the conclusion that fatigue distinctly aided the development of the infectious diseases in inoculated animals. The fatigued animals died much more quickly than those left alone, and sometimes these latter got well. The experiments seemed to show that it was not individual predisposition, but the prolonged fatigue, that determined the moment of yielding to the disease.

Canalis and Morpurgo demonstrated the effect of starvation in increasing the susceptibility to infectious diseases. They took up the subject again by studying in birds the influence of inanition that Gibier had studied in frogs. They used as the experimental animal the pigeon, which is neither very susceptible nor very refractory to anthrax. Of the birds that they used, but two out of twelve died after being inoculated with anthrax. The inoculation was made by introducing under the interior face of the wing, previously sterilized, a dose of an agar culture of anthrax full of spores, virulent to rabbits and guinea-pigs. The result of the inoculation is very different if the pigeon be subjected to fasting for several days before the injection, or only at the time. Of sixteen pigeons thus inoculated, fifteen died with anthrax bacilli in all the organs (muscle, heart, liver, spleen). The sixteenth was a pigeon that had been fasting for seven days and died the day after the inoculation, doubtless of hunger, but there was seen a marked development of the bacilli at the point of inoculation. Other birds of the same species, on the other hand, resisted the inoculations with anthrax if food was given them at once after the injection, provided the effect upon their health was not too profound. Of ten birds that had fasted for six days before the inoculation, which were fed immediately after it, not one died; but of four that were inoculated after seven days of fasting, two died. Before attributing to starvation alone these curious effects, the authors considered whether a portion of them might not be due to the natural fall of temperature that is the result of inanition. In order to determine this, they placed the inoculated pigeons in a bath at about the same temperature below normal that they would have were they in a condition of inanition. Nine animals thus treated died, but not one of anthrax; no bacilli were found in the organs, and the local reaction at the

point of inoculation was as slight as in refractory pigeons. Canalis and Morpurgo therefore considered themselves justified in concluding that the cooling had nothing to do with the fatal results after inoculation with anthrax, but that these were due entirely to the fasting. Possibly it will be necessary to modify this conclusion somewhat in considering the mechanism of death. A physiological influence is not like a brick in a wall that can be broken or taken out without injuring the remainder. It would be extremely remarkable if an exposure to cold that of itself could produce death should not have some effect upon the resistance to anthrax; possibly this influence is not direct, and is effected by the intermediary of the white corpuscles, as shown by Wagner in his work upon the anthrax of chickens.

This restriction upon the causes does not of course alter the facts that seem to be well authenticated. Canalis and Morpurgo attempted to utilize this susceptibility of fasting birds to anthrax to determine the length of time that the virulence of the bacilli introduced under the skin would last. For this purpose it was enough to stop the food some days after the inoculation, and to see what would become of the birds that up to that time had remained healthy, for if they became affected with anthrax, it would be because they had preserved some living anthrax bacilli at the site of the inoculation. Operating in this way, it was found that of twelve pigeons subjected to fasting on the fifth day after the inoculation all died of anthrax, and there were many bacilli in the blood; of two fasting on the seventh day, one died, and the condition of the other was doubtful; but of five fasting eight days, two became affected with anthrax. Beyond this limit none became infected, and none died except from the effects of the prolonged fasting to which they were subjected in waiting for the appearance of the symptoms of anthrax. This ingenious experiment is in accord with the results of Metchnikoff, proving that the bacilli introduced into the bodies of refractory pigeons retained there their vitality and their virulence for a long time. Canalis and Morpurgo were not satisfied with experimenting upon pigeons, but used also chickens and white rats. They found with chickens, as did Pasteur, that fasting did not make them more susceptible to anthrax if they were inoculated before inanition, but that if the fasting were begun eight, seven, four, or even three days before the inoculation, about half (seven out of twelve) died of anthrax three to eleven days after inoculation. With white rats, in which the susceptibility to anthrax appears to be variable (Metchnikoff), fasting never seemed to have any perceptible effect. Canalis and Morpurgo also studied the effect of the complete extirpation of the pancreas, and determined that this

operation produced at least a temporary increase of susceptibility to anthrax.

The behavior of muscular tissue in infectious diseases is well demonstrated by Giacomo. Two sorts of investigation were made, one to determine the condition of muscular tissue in the infectious diseases, and the other the bactericidal power of muscle fluid taken under aseptic conditions.

For the first, the infectious materials (anthrax bacillus, staphylococcus aureus, micrococcus tetragenus) were injected into the jugular vein in rabbits and guinea-pigs; sometimes the death of the animal was waited for, and sometimes this was secured by chloroform, and then small portions of the muscular tissue were taken from the gluteus muscle, the spleen, kidney, and liver, under antiseptic precautions. These were divided by crushing in distilled water, and then plate cultures were made, and it was shown that there were many less bacilli in the muscle than in the organs, and sometimes (in the case of the anthrax bacillus and of streptococcus aureus) the muscle was found to be entirely free. It was also observed that an hour after the injection it was possible to demonstrate many more bacilli in the muscle than later, and that after eight hours there were no more bacilli to be found. This bactericidal action of the muscular tissue could also be demonstrated with non-pathogenic bacteria.

For the second research, there was taken muscle fluid from dogs, rabbits, and horses. The animals were killed by bleeding, and portions of the muscle were taken from various parts, cut into small pieces, and then squeezed in a sterilized press. It was shown by experiment that the fluid was sterile. The research as to the bactericidal action of the fluid was carried on with typhoid and cholera bacilli, and this action appeared to be marked for all three species of animals, especially dogs; after four hours the vitality of the bacteria that had been introduced into this muscle fluid was completely destroyed. The bactericidal property was in accord with the size of the mixing, and after four days the loss of it was not apparent in the fluid from dogs, as is the case with blood serum. It cannot be said that it is the acid reaction that causes the bactericidal action of the fluid, for it remains after the addition of a neutralizing soda solution. Neither does the author consider that the higher concentration of the fluid has anything to do with it, but he thinks it more likely that it is due to some modification or condition of the albuminoid bodies as the active principle.

Rôle of the Nervous System.

The part played by the nervous system in bacterial infections is probably an important one. The work of Virchow, Samuel, Charrin, Roger, Gley, Bouchard, Herman, and others, has shown the great influence of the nervous system on inflammatory processes and bacterial infection. But this work is very incomplete, and at present the facts at hand are not sufficient to permit the formulation of a theory concerning the influence of the nervous system upon the infectious processes.

Dache and Malvoz report a number of experiments that have a bearing upon the question, although they are not able as yet to give the exact explanation of them.

Starting from the notion that in general the inoculation of specific bacteria in a resisting animal provokes especially a local reaction, while in the susceptible races the bacteria become generalized, most often without any marked local reaction, the question arose whether the increase of the local reaction produced by the section of the nervous supply to the part might not be a useful factor in the protection of the system against the invasion in the habitual conditions of experimentation. It was in attempting to solve this question that the important result was arrived at that nerve section in animals susceptible to anthrax made them much more susceptible to protective inoculations, and likely to benefit by them.

C. K. Mills, in a very exhaustive review of the subject, comes to the following conclusions: 1. Specific infection must be included among the causes of mental diseases and of symptoms which precede, accompany, or follow febrile or other infectious disorders. 2. Much negative evidence can be adduced in favor of acute delirium or acute mania being due to toxæmia, such evidence as is afforded by autopsies which reveal neither gross nor histological lesions; and in these cases the toxæmia probably overwhelms the patient before the production of meningitis or other disease. 3. Analogies with nervous affections which are known or believed to be of microbic origin, such as multiple neuritis, myelitis, and chorea, favor the view that insanities with similar or related phenomena and lesions are also microbic in origin. 4. The evidence afforded by careful bacteriological investigations of cases of acute insanity is thus far meagre, but shows that various microorganisms may induce the same or similar types of mental disease. 5. The mental disorders of pregnancy and the puerperal state are probably, in a considerable proportion of cases, toxæmic, without reference primarily to childbirth; but it cannot be

regarded as proved that a bacillus of either eclampsia or puerperal mania is the sole cause of these affections.

Finally, J. J. Putnam summarizes the relation of infectious processes to diseases of the nervous system, as follows: It is important to separate (*a*) the symptoms and lesions which we can assert to be directly due to the specific toxins of the various infective diseases, from (*b*) the effects of anæmia, œdema, intoxication from disordered metabolism on the one hand, and on the other hand from (*c*) the affections which spring into existence because the nervous system was prone to them, either from peculiarities of structure, anatomical surroundings, circulation, and the like, or because other causes had been at work to which the infective poison only contributed new effectiveness for evil.

In the first class (*a*) we can fairly place the symptom groups of tetanus and rabies, and with reasonable probability the chill, pains, paræsthesias, acute delirium, disorders of micturition, and other symptoms which characterize the outbreak of many acute febrile disorders, though it must be admitted that we know little or nothing about their pathogenesis.

The focal hemorrhagic encephalitis and myelitis occasionally observed after influenza and other infectious processes is probably due to the action of the specific poison on the tissues and the vessels. Acute poliomyelitis and acute hemorrhagic nephritis may be of the same origin, though these opinions need further substantiation.

As regards tetanus and rabies, it is not probable that the anatomical lesions which have been found after death (Golgi and others) are actually the anatomical substratum of the characteristic symptoms. They may have been simply of correlative origin.

Post-infection meningitis is generally of a purulent character, and implies the presence of microorganisms; but the non-purulent form bears a relation to infectious disease which is in need of further study.

The paralyses of diphtheria are probably attributable to the direct action of the poisons, but, as in the case of tetanus and rabies, it is by no means certain that the lesions sometimes found (though often missed) are the true cause of the symptoms. It is more probable that the first and characteristic effect of the poison is to excite a chemical or molecular change, and that this alone is strictly characteristic. Sometimes the paralysis passes away too rapidly to be attributable to neuritis. The lesions when present may be many and various, and the neuritis, which is the commonest form, is of varying types.

The lesions met with in meningitis, and in a certain sense those characteristic of tuberculosis and syphilis, are directly due to bacterial action.

In the following cases, the influence of cause *a* is more or less combined with those of causes *b* and *c*.

The question as to the origin of the post-infection multiple neuritis is one of great interest. The most obvious position to take is in favor of its direct dependence on the infective poison; but in view of the general fact of the intolerance of the peripheral nerves to poisons of all sorts, it is fair to suspect that the post-infection neuritis may sometimes be due to toxic substances developed from impaired metabolism, and sometimes to anæmia and œdema (class *b*).

It appears to be occasionally possible to induce neuritis by experimental inoculation with diphtheritic cultures, and the form and sequence under which the diphtheritic paralyses clinically occur suggest the action of a specific poison. If, however, the forms under which neuritis typically occurs are considered, it becomes obvious that natural proclivities of the nervous system are at least contributive causes.

The variety of conditions under which spinal scleroses, both disseminated and systemic, occur suggests predisposing tendencies of one or another kind, common to all, and acting in addition to the various special causes. The observations of Obersteiner and Redlich, that the narrowing of the posterior nerve roots at their point of penetration through the pia mater suggests a mode by which slight pressure (as from syphilitic meningitis) could set up the ascending degeneration characteristic of tabes, do not afford a complete explanation of that disease. This theory leaves unnoticed the close analogy between the syphilitic tabes of the lateral columns and that of the posterior columns. The occurrence of the peripheral neuritis met with in connection with syphilitic tabes, but rarely seen at other stages of syphilis, points to the presence of some poison as yet undiscovered, and strengthens the probability that the posterior-column degeneration of anæmia and ergot poisoning, as well as that of syphilis, is mainly of toxic origin.

The complex nature of the infective poisons is shown by the varying relations between the toxic symptoms of the first stage (fever, delirium, pain, etc.) and those of the later stages.

In influenza the fever may be of trifling amount and duration, and yet the post-infective diseases may be severe and lasting; in cerebrospinal meningitis the fever is often slight. Again, it has been found possible, experimentally, to neutralize to a certain extent the fever-producing element in bacterial poisons by special antitoxins (Centanni and Bruschettini).

Finally, it is probable that a routine examination, by the best modern methods, of the central and the peripheral nervous systems

after infection, would show changes to be present far oftener than is now supposed. The studies of Golgi in rabies lend support to this view.

As an additional contributive cause of lesions, fatigue may be mentioned, since the experiments of Hodge show that this is capable of exciting manifest changes in the nerve cells. It is a question for further investigation, whether or not fatigue acts more forcibly on nerve centres poisoned by the products of infectious processes.

Periods of Incubation and Infectiousness.

Broadbent and Dawson Williams were appointed in 1888 by the Clinical Society of London a committee to investigate the subject of the period of incubation and of transmissibility of the principal infectious diseases, and reached the following conclusions: In diphtheria the period of incubation is most frequently two days, usually does not go over four days, and rarely exceeds six or seven days; over seven days is doubtful. Most frequently the disease is acquired by personal contact with persons affected with the disease or with convalescents; the possibility of the infection during the incubation period is also apparently established; the convalescents are often infectious for a long time, as is shown of late years by the cases of persistent bacilli that are so common since the introduction of the bacterial diagnosis of the disease. The diphtheria virus remains in clothing and other places for months and perhaps for years. In typhoid fever the period of incubation lasts usually for twelve to fourteen days, rarely as short as seven days; there are observations showing that it may last as long as fourteen, eighteen, or twenty-three days. The convalescent remains infectious for fourteen days after the beginning of convalescence; the poison sometimes lasts in the effects of the sick for two months. Influenza has a period of incubation of three to four days; the affected person may transmit the disease for eight to ten days after the appearance of the first symptoms. In measles the incubation lasts for an average of nine to ten days to the appearance of the rash, but varies from five to fourteen days; its infectiousness lasts for about fourteen days after the breaking out of the rash, but the infectiousness of the effects of the patient lasts for only a short time. Incubation in scarlet fever lasts usually for twenty-four to sixty-two hours, but is often prolonged four, five, six, and seven days. The individual remains infectious for two months; the poison remains easily in the clothing of the sick.*

* These interesting points are discussed in detail in the article on "Periods of Incubation and Infectiousness" in the present volume.

Prevention of Infectious Diseases.

The management of infectious diseases in war is summarized by R. Koch, who divides the prophylactic measures to be taken against the infectious diseases into two groups, in which the measures to be taken against any special disease may be included. He confines himself, however, to the consideration of but one in this article. His conclusions are the following: The infectious diseases are the same as the parasitic diseases; they are not produced by miasms but by definite formed elements. The infectious diseases are propagated only by the growth of their specific cause, never by bad hygienic surroundings; these last can only be active in helping on the growth of the specific cause. The change of one infectious disease into another is not possible. The varying intensity of the individual illnesses in the course of an epidemic is due to the variation of virulence in the different phases of the epidemic.

As the bacteria retain their vitality for a long time in the dried condition, so also they find favorable conditions for their growth only in a proper supply of moisture. First, then, when these fluids as such are pulverized, or when they have been dried and then powdered, the microorganisms cannot grow until they have been carried by the dust to some place where they receive sufficient moisture for their development. The air, however, is much less to be considered as a carrier of infectious diseases than fluids, and especially water.

Moisture on the surface of the earth makes this a good ground for the development of the microorganisms, while deeper down, in spite of the increasing moisture, the lower temperature makes it an unfavorable place.

We should, therefore, prevent as far as possible the drying and pulverizing of the infectious material, or at least the escape of this dust into the inhabited places of men must be prevented. The method of preventing this is the proper ventilation of the rooms which are devoted to the care of those sick with infectious diseases.

Ground-water is to be considered only so far as the infectious material may pass into it through crevices in stone or gravel which do not filter, and thus may get into the drinking-water.

Some infectious materials can live only in the body, and are carried either by actual contact or else in dust form through the air. Others may live and grow outside of the body as well; and of these some live better in water, others in the earth.

Prophylactic precautions against the infectious diseases must be

organized with especial reference to these peculiarities of the disease being dealt with. Before the outbreak of an epidemic the precautions to be taken are general, and have reference to the surroundings of the persons it is sought to protect; in especial must the ventilation of the rooms be attended to. The earth must be dry at its surface, and everything that by any possibility could hold infection must be kept away from the ground. Especial attention must be paid to the water supply, as well as to the cleanliness of the rooms, the clothes, and the bodies of the men.

Once an epidemic is started, the attack must be directed against the infectious material itself. To this end, the first case is of the utmost importance, and to determine this the microscopical and bacteriological examination is of the most vital importance. The first case must be absolutely isolated, and the possibility of the transportation of the infectious material must be prevented, which is to be done in the first place by disinfection, and finally even by burning.

If it should happen that we are not called in at the beginning of an epidemic, it must be fought with all the general and special rules that a military organization allows.

Smallpox is to be combated, of course, by universal vaccination with proper virus.

IMMUNITY.

After infection and its causes, there come up for consideration the facts of immunity, its probable causes and conditions. That a condition of immunity, meaning by that a resistance of the living organism to infection, does exist, is axiomatic. The causes of its existence are, however, not so well understood as they should be. In regard to the general subject, MacFarland says that "one of the most astonishing facts observed in comparative pathology and physiology is the resistance which certain animals and classes of animals, not differing very much from other animals, but often differing very widely among themselves, show to the invasion of their bodies by the germs of disease. Thus, man suffers from typhoid fever, cholera, and other infectious diseases, which are never observed in the domestic animals; cattle are subject to a pleuropneumonia, which does not affect their attendants; man, the cow, and the guinea-pig are especially susceptible to tuberculosis, which the cat, dog, and horse resist; yellow fever is a highly contagious, infectious disease, which is almost certain, when epidemic, to attack all new arrivals of the human species but which rarely, if ever, attacks animals.

"The popular mind accepts a statement of such facts as these without any other explanation than that the animals are different. The

more the professional man contemplates these facts, however, the more complicated the matter becomes; for while it might be admitted that a difference in the bodily temperature and chemistry might explain why a frog will resist anthrax which readily kills a common rat, it will not explain why a white rat, whose chemistry must be almost if not quite identical with that of the house rat, can successfully combat the disease. Nor is this all. The fact that one attack of yellow fever, of typhoid fever, or of scarlet fever renders a second attack almost impossible is not the less interesting because it is of almost daily observation. The mouse which has recovered from tetanus will not take tetanus again, and most interesting and extraordinary is the fact that a few drops of blood from the recovered mouse, injected into another mouse, will protect the latter from future attacks of tetanus."

The condition in which the body of an animal resists the entrance of disease-producing germs, or, having been compelled to allow them to enter, resists their growth and pathogenesis, is called "immunity." The resistance so manifested is a distinct, potential, vital phenomenon.

The opposite condition, in which instead of resistance there is a passive inertia which allows the disease-producing organisms to develop without opposition, is called "susceptibility." Susceptibility is accordingly seen to be nothing more than the absence of immunity. Immunity is either natural or acquired.

Natural Immunity.

By this term is meant the natural and constant resistance which certain healthy animals exhibit towards certain diseases which affect other kinds.

The white rat is peculiar in resisting anthrax. It is almost impossible to develop anthrax in a healthy white rat, but Roger found that such an animal would easily succumb to the disease if compelled to turn a revolving wheel until exhausted. Susceptibility which follows such an exhaustion of the vital powers cannot be regarded as other than accidental, and makes no exception to the statement that the white rat is immune to anthrax. Animals such as man, sheep, cows, and rabbits are susceptible to anthrax, while birds and reptiles are generally immune. The great difference in the morphology between mammals, and birds and reptiles, together with the fact that their temperature, blood, and tissues all differ, makes this immunity reasonably intelligible. Morphological differences, however, will not suffice to explain all cases, for the Caucasian nearly always succumbs to yellow fever, while the negro is more rarely affected,

and scarlatina, which is one of our commonest and most dangerous diseases of childhood, is said to be unknown among the Japanese. Nor is this all, for close as is their resemblance in all respects except color, the house mouse, the field mouse, and the white mouse differ very much in their susceptibility to various diseases.

Acquired Immunity.

By this term is understood a resistance which is the result of accidental circumstances. Most of us have suffered from rubeola, scarlatina, and varicella, and in consequence of the attack are now immune. One attack of yellow fever is always a complete guard against another. Typhoid fever is rarely followed by a second attack.

Sometimes the immunity is experimentally produced, as when by vaccination we produce the vaccine disease, and afterwards resist variola. Acquired immunity is a little less complete, and not so permanent as natural immunity, for in the latter, it is only when the functions of the individual are disturbed or his vitality is depressed that the resistance is lost, while in the former, time seems to lessen the power of resistance so that rubeola and scarlatina may return in a few months or years, and for complete protection vaccination may need to be done as often as every seven years.

Experimental Immunity.

Immunity may be produced experimentally in various ways.

Operations upon the Animals.—The house mouse and the white mouse are susceptible to tetanus. If from a convalescent or a tetanic mouse a drop or two of blood be injected into another mouse, it is said to render it immune.

Manipulation of the Specific Organism.—Pathogenic bacteria are possessed of powers which are described as virulent, and which generally weaken very much when the bacteria are grown upon artificial media. This condition of weakened virulence is called *attenuation*, and may be produced by: (1) Cultivating the bacteria upon media containing 1:5,000 to 1:2,000 of bichromate of potassium, or one per cent. of carbolic acid; (2) cultivating them under a pressure of eight atmospheres; (3) cultivating them, and exposing the cultures to sunlight for a short time; (4) exposing the cultures for ten minutes to a temperature of 55° C. After subjection to manipulations such as these, the most virulent of the bacteria will often be so attenuated as to cause little or no disturbance when inoculated into susceptible animals.

In passing, it is well to call attention to a curious result which very frequently follows the introduction of attenuated microorganisms into susceptible animals, viz., the production of immunity to the virulent form of the organism.

Combining Various Microorganisms.—Pawlowski found that when rabbits, which are very susceptible to anthrax, are simultaneously injected with the bacillus anthracis and the bacillus prodigiosus, which is harmless, they recovered from the anthrax, as if the harmless microbe possessed the power of neutralizing the poison of the other.

Destruction of Immunity.

Immunity may be destroyed in numerous ways.

Variation from the normal temperature of the animal under observation. Pasteur observed that chickens would not take anthrax, and suspected that it might be due to their high body temperature. After inoculation he plunged the birds into a cold bath, thus reducing their temperature, and succeeded in destroying their immunity. The experiment was a success, but the reasoning seems to have been faulty, as the sparrow, whose temperature is equally high, readily falls a victim to anthrax without a cold bath.

In various specific fevers the temperature curve is interesting, rising steadily as the bacteria grow vigorously until a maximum is reached, then falling abruptly at the same time that the activity of the microorganisms begins to wane. Whether these activities cease because the high temperature attained is prejudicial to the growth of the bacteria or because their own products injure the bacteria is still a question; probably the latter view is the correct one.

Altering the chemistry of the blood by changing the diet, or by hypodermic injection. Leo found that when white rabbits were injected with phloridzin, and also when they were fed with phloridzin, an artificial glycosuria resulted which destroyed their natural resistance to anthrax. Platania succeeded in producing anthrax in dogs, frogs, and pigeons, naturally immune, by subjecting them to the influence of curare, chloral, and alcohol.

Diminishing the Strength of the Animal.—Roger, by compelling white rats to turn a revolving wheel until exhausted destroyed their immunity to anthrax.

Removing the Spleen.—Bardach has shown how greatly the chance of recovery from specific diseases is lessened by the removal of the spleen.

Combining different species of bacteria, either of which, when injected alone, would be harmless or of slight effect. Roger found that

when animals immune to malignant œdema received a simultaneous injection of 1 or 2 c.c. of a culture of bacillus prodigiosus and the bacillus of malignant œdema, they would contract the disease.

Sometimes an apparent immunity depends upon the attenuation of the culture used for inoculation, and the erroneous results to which such a mistake would lead are obvious. Should a culture become attenuated, its virulence may be increased by inoculating it into the most susceptible animals, then from these to less susceptible, and from these to an immune animal. The virulence of anthrax is increased by inoculations into pigeons, and also by cultivation in an infusion of the flesh of an animal similar to the one to be inoculated.

It must be understood that the term immunity is a relative one, and that while a white rat is immune against anthrax in amounts sufficiently large to kill a rabbit, it is perhaps not immune to a quantity sufficiently large to kill an elephant.

Theories of Immunity.

It is not to be expected that such intricate phenomena as these which have been mentioned could be observed and suffered to go unexplained. Alas! we have explanations, but they are as intricate as the phenomena, and, though each may possess its grain of truth, not one will satisfy the demands of the thoughtful student. In brief review, these theories are the following:

The Exhaustion Theory.

This was advanced by Pasteur in 1880, and teaches that by its growth in the body the microorganism uses up some substance essential to its life, and that when this substance is gone the microbe must die. The removal of this substance, if complete, will give permanent immunity.

In his "Manual of Bacteriology" Sternberg gives a very just criticism of this theory. Were it true, he says, we must have within us a material of smallpox, of measles, of scarlet fever, etc., each of which must be exhausted by its appropriate organism. It would necessitate an almost inconceivably complex body chemistry, and a rather stable condition of the same.

The Retention Theory.

In the same year Chauveau suggested that the growth of the bacteria in the body might originate some substance prejudicial to their further and future development. There seems to be a large kernel of truth in this, but were it always the case we should have added

to our blood a material of smallpox, of measles, of scarlet fever, etc., so that we should become saturated with the excrementitious products of the bacteria, instead of having so many substances subtracted from our chemistry.

Phagocytosis.

In 1881 Carl Roser suggested a relation between immunity and the already familiar phenomenon of phagocytosis. Sternberg in this country and Koch in Germany observed the same thing, but little real attention was paid to the subject until 1884, when Metchnikoff appeared with his careful observations upon the daphnia, as the great champion of what is now known as "Metchnikoff's Theory of Phagocytosis."

Phagocytosis is the swallowing or incorporating of foreign particles by certain of the cells which are called phagocytes. This activity of the cells towards inert particles had been observed by Virchow as long ago as 1840, and towards living bacteria by Koch as early as 1878, but was not carefully studied until Metchnikoff advanced his theory in 1884. By Metchnikoff, the phagocytes are divided into fixed phagocytes, comprising the fixed connective-tissue cells, endothelium, etc., and the free phagocytes. The terms phagocyte and leucocyte are not to be regarded as synonymous in this connection. "Of the leucocyte there are several varieties, one of which is immobile, and never takes up bacteria. This is the lymphocyte, characterized by its small size, its single large nucleus, and small amount of surrounding protoplasm. The two remaining phagocytic forms are, first, the large unicellular leucocyte, whose prominent nucleus is at times lobed or reniform, which stains well with the aniline dyes, and possesses much protoplasm and active amœboid movements—the *macrophagocyte;* and, second, the *microphagocyte*, a small form, also staining well, but either multinuclear or with one nucleus in process of breaking up."

It is obvious that only those cells are phagocytes that possess amœboid movement. When an amœba, in a liquid containing numerous diatoms and bacteria, is watched through the microscope, an interesting phenomenon is observed. The amœba will approach one of the vegetable cells, even though it may be at a distance, will apprehend it, and within the animal cell the vegetable cell will be digested and assimilated. The amœba has no eyes, no nose, no volition, and so far as we can determine, no nervous apparatus which gives it tactile sense; yet it will approach the particle fitted for its use and englobe it. The attraction which draws the animal cell to the vegetable cell in this illustration is called *chemotaxis.*

Chemotaxis is the exhibition of an attractive force between amœboid cells and food particles. This attractive force, when operating so as to draw the amœba to the particle it will use, is further named *positive chemotaxis*, in order to distinguish it from a repulsive force sometimes exerted (?), causing the amœboid cells to fly from an enemy, as it were, and which is called *negative chemotaxis*.

The force which guides and operates the amœba in its movements is exactly the same as that which governs the movement of the phagocytic cells of the human body, and observation of these phenomena is not difficult. If a small capillary tube be filled with sweet oil and placed beneath the skin, only a short time will pass before it will be found full of leucocytes—positive chemotaxis. If, instead of sweet oil, oil of turpentine be used, not a leucocyte will be found—negative chemotaxis, or, more correctly, no chemotaxis at all.

Phagocytosis is almost universal in the microorganismal diseases at some stage or other. If the blood of a patient suffering with relapsing fever be studied beneath the microscope, it will be found to contain numerous actively moving spirilla, all free in the liquid portion of the blood. As soon as the apyretic stage comes on, not a single free spirillum can be found. All of them are seen to be enclosed in the leucocytes.

At the edge of an erysipelatous patch a most active warfare is being waged between the streptococci and the cells. Near the centre of the patch there are many free streptococci and a few cells. Nearer the margin there are free streptococci and also a great many streptococci enclosed in cells (leucocytes) which are for the most part dead. Further out we find hosts of active living cells engaged in eating up their enemies as fast as they can. The phagocytosis proves that at the centre the bacteria are fortified, actively growing and virulent. In the next zone the leucocytes that have feasted upon the bacteria are poisoned by them. Outside, the cells which are more powerful and which are constantly being reinforced are waging successful warfare against the streptococci. In this manner the battle continues, the cells now being obliged to yield to the bacteria, and the patch spreading, while the cells subsequently reinforce and destroy the bacteria, so that the disease comes to a termination. Metchnikoff introduced fragments of tissue from animals dead of anthrax under the skin of a frog, and found them surrounded and penetrated by leucocytes containing many of the bacilli.

Chances of error exist in all these cases. The bacteria may have been dead before the cells ingested them, and the digestion and destruction that has gone on in their interior may have been the digestion of dead bacteria. In the relapsing-fever illustration, the exception

may be taken that the apyrexia may have marked the death of the spirilla, which were taken up by the leucocytes only when dead. In the erysipelas illustration the streptococci remote from the centre of the lesion may have met, through the action of the body juices or some other cause, a more speedy death than that from the digestive juices of the leucocyte.

Metchnikoff, however, showed that the leucocytes do take up living pathogenic organisms. He succeeded in isolating two leucocytes, each containing an anthrax spore. These he conveyed to artificial culture media, and watched. The new environment being better adapted for the growth of the bacterium than for the leucocyte, the latter died, and the spore developed into a healthy bacillus, under his eyes, showing that the leucocytes do take up virulent living organisms. Seeing that the animal cells do take up bacteria, and seeing that the amœbæ can ingest and digest threads of leptothrix ten times as long as themselves, we need only put two and two together to see that Metchnikoff's theory rests upon a very substantial foundation. The more virulent the bacteria are the less ready the leucocytes are to seize them. The more immune the animal is the greater the affinity of the leucocyte for the bacteria.

The organisms which are seized upon by the leucocytes do not remain in the blood, but are collected in the spleen and lymphatic glands; and not the least important fact in favor of phagocytosis is that observed by Bardach, that excision of the spleen diminishes the resistance to infectious diseases.

Quinine also furnishes a therapeutic support to the theory. It is known that quinine increases the destruction of leucocytes. Woodhead inoculated a number of rabbits with anthrax, giving quinine to some of them. Those that had received the drug died earliest, a fact probably caused by the destruction of part of the phagocytic army.

Ruffer found that the phagocytes exercise a distinct selective tendency between various kinds of organisms. They will leave the bacillus of tetanus in order to seize upon the bacillus prodigiosus, if simultaneously introduced; also the streptococci in diphtheria for the Klebs-Loeffler bacilli. This is illustrated in the diphtheritic membrane, where at the surface one can see leucocytes taking in numbers of the bacilli, but leaving the streptococci almost untouched, with the immediate result that the streptococci are often found in the deeper parts of the membrane, and with the remote result that secondary abscesses occurring in the course of diphtheria are never due to the bacillus of diphtheria, but to some other organism.

In order to satisfy sceptical minds of the truth of the destruction of microorganisms by the bacteria, Metchnikoff made a special study

of tuberculosis. Observing that it seemed true of all bacteria, that the more perfect they were the more sudden their death for examination purposes, and the more virulent their properties the more brilliantly they take aniline dyes, he made use of this to show the action of the cells upon the tubercle bacillus. A species of marmot, called the *Zieselmaus*, is almost perfectly immune to tuberculosis, and when a culture of tubercle bacilli is injected into its abdominal cavity the bacilli are taken up by the epithelioid cells, and later appear enclosed in giant cells. Metchnikoff shows that the bacilli in the epithelioid cells and those few lying free in the tissue stain well, but that those contained in the giant cells are surrounded by a yellowish, scarcely tingible halo, which he describes as a cheesy degeneration of the bacillus caused by the action of the cell juices upon it, and concludes from this that the giant cells of tuberculosis are enormous phagocytes. This is an extremely interesting and important contribution to the question of phagocytosis, the only misfortune being the fact that Baumgarten and Weigert were unable to substantiate it in their researches.

Wyssokowitch found that saprophytic microorganisms were quickly eliminated from the blood when injected into the circulation. This elimination was not by excretion by organs, nor by destruction in the bloodstream, but by the collection of the organisms in the small capillaries where the blood stream is slow, and where the microorganisms are taken up by the endothelial cells. Wyssokowitch found them most numerous in the liver, spleen, and bone marrow, and found that in these situations they were destroyed in a short time, the saprophytic organisms in a few hours, the pathogenic in from twenty-four to forty-eight hours. Living spores of the bacillus subtilis remained as living entities in the spleen for three months.

The Humoral Theory.

Some new observations, however, inaugurated a new epoch in research, and a new theory of immunity. It was observed that if a few anthrax bacilli were introduced into a few drops of rabbit's blood they were instantly killed. This observation was one of immense importance, and from it and similar observations Buchner deduced the principles of his theory, that the destruction of pathogenic bacteria in the body is due to the bactericidal action of the blood plasma, not to phagocytosis, which in his eyes amounts to nothing more than the burial of the dead bacteria "in cellular charnel-houses." The experiments of Buchner and his followers have shown that freshly drawn blood, blood plasma, defibrinated blood, aqueous humor, etc.,

possess marked destructive influence upon the organisms brought in contact with them, a property which is easily destroyed by heat.

The apparent paradox of rapid multiplication of anthrax bacilli in the rabbit's blood, enclosed in the rabbit's body, and the reversed action in the test-tube caused immediate and prolonged opposition. Each side of the controversy seemed to be well supported. The phagocytists, however, showed that bacteria were often injured and their vegetative powers often destroyed by sudden changes from one culture medium to another, this being proved by Haffkine. In experimenting with aqueous humor, Metchnikoff has shown that its germicidal action is largely imaginary, and due to the dispersion of the organisms in a large amount of watery fluid. When the microorganisms are introduced into it in such a manner as to remain together they grow well. If the tube be shaken they die. Again, Adami has shown that when blood is shed there is almost always a pronounced destruction of corpuscles, and suggests that the antibiotic property of the shed blood may be due to a solution of the substances formerly in the protoplasm of the leucocytes.

Wyssokowitch surely argued against a humoral germicide just as much as against phagocytism when he showed that spores of bacillus subtilis could reside in the spleen for three months uninjured.

In defending their theory, the humoralists experimented by placing microorganisms, enclosed in little bags of pith, collodion, etc., beneath the skin. These bags would allow the fluids of the body free access to the bacteria, but would shut out the leucocytes. By this means Hueppe and Lubarsch have repeatedly seen the bacteria grow well, while Baumgarten has failed to find this the case. Such experiments are by no means conclusive, for we should remember that the necessary operation and the presence of the foreign body in which the bacteria are encased produce an inflammatory transudate which may have very different properties from the normal juice.

How much of the immunity which animals enjoy depends upon the bactericidal action of their body juices must remain an open question. Certain it is that in some cases the germicidal action of the blood is unquestionable.

The greatest stumbling-block in both the phagocytic and the humoral theories remains to be mentioned. How is acquired immunity to be explained? We might conceive the phagocytes or the blood plasma capable of destroying the parasites, but how shall this make clear to us why, after an attack of a disease, or how, after protective inoculation, these phagocytes or this plasma acquire the formidable antibiotic properties which will in the future protect the individual previously susceptible? Both schools attempt a fallacious

explanation which is no explanation at all. The phagocytists tell us that after the microorganisms have been met and defeated by the phagocytes, these cells develop a peculiar appetite for germs of this kind, and also a peculiar tolerance to their pathological products. The humoralists teach us that, the body having become accustomed to the poison produced by the parasite, the latter is now to it only a simple parasite, easily destroyed by its juices. Both these explanations simply assert that the body becomes tolerant and resists the inroads of the germs, nothing more. Probably because of the necessity for a satisfactory explanation of the above phenomena, a new school gradually arose, inculcating the doctrine of

Defensive Proteids.

According to this theory the metabolism of bacteria gives rise not only to poisonous substances called *toxins*, but also to other substances possessed in part of the property of neutralizing them, called *antitoxins*. The most extensive researches in this field have been made by Hankin, who found in the bodies of immune animals proteid substances possessed of distinct properties in relation to bacteria. These substances had previously been pointed out by Buchner as *alexins*, but Hankin found it more convenient to divide these compounds into certain groups, as follows: Proteid substances which occur naturally in normal animals, and are possessed of the power of destroying either the virulence of bacteria or their products, he calls *sozins*. Similar proteid substances possessed of similar properties, but occurring in animals having acquired immunity, he calls *phylaxins*. Each of these is divided into two classes, so that a sozin possessed of the property of killing bacteria is called a *mycosozin*, while a sozin which neutralizes bacterial products is called a *toxosozin*. In the same way a phylaxin which kills bacteria is called a *mycophylaxin*, while one that neutralizes their ptomaïns is called a *toxophylaxin*.

The Klemperers produced immunity against pneumonia which lasted six months in animals, by the injection of filtered cultures of the pneumococcus. They believe "that the immunity depends on antitoxins, built up in the tissues under the stimulation of the injected fluid; not that this antitoxin was injected with the filtrate of the cultures."

Whatever these immunizing substances are, it sometimes seems that they pass into the secretions. Ehrlich injected into a nursing mother-mouse a few drops of blood from a horse immune against tetanus, and observed that the baby-mice became immune through the

mother's milk, one of them surviving inoculation from a splinter that sufficed to kill a much larger mouse.

The application of the knowledge of these antitoxins, however, does not always bring success with it, and a great disappointment has resulted from an attempted therapy of pneumonia based upon the supposition that the crisis in this disease was due to the neutralization of the pneumotoxin by an antitoxin, and that consequently, if some of the blood from a convalescent patient were injected into one in the early stage of the disease, crisis should result.

A great attack upon the toxin and antitoxin theory has recently been made by Charrin, Gamaleïa, and Selander, whose careful investigations show that the toxins are so little attacked by antitoxins in the immune animals in septicæmia, caused by the vibrio Metchnikovii, pyocyanic disease, and hog cholera, in the rabbit, that the same quantity of the toxin in solution suffices to kill the protected animal as causes death in the susceptible. This shows that it is the microorganism itself rather than its products which the animal is able to resist, and again brings us to the starting-point of our discussion, with no other positive knowledge of immunity than that in some way immune animals are able to combat and destroy virulent bacteria, and to annul the influence of their poisonous products (McFarland).

Summary of Cheron.

Cheron summarizes the theories of immunity as follows: Immunity, or the power of the organism to defend itself against an infection, may be either natural or acquired. A great number of theories since the discovery of the bacteria have been suggested to explain the mechanism. Many have only an historical interest, and these need not detain us; three are actually under discussion, and should be studied in detail. These are the theories of phagocytosis, of the bactericidal power of the blood, and of the antitoxins.

Phagocytosis.—The theory of phagocytosis is entirely due to Metchnikoff, and according to him is about as follows: Phagocytosis is exerted by the leucocytes or white corpuscles of the blood or lymph, of which he has made out several varieties. The *lymphocytes* are small leucocytes with a large nucleus surrounded by a small amount of cell protoplasm; they are very numerous in the lymph, and present all degrees of passing to the larger leucocytes called *mononuclear leucocytes*, and which often have a kidney or bean-shaped nucleus. The *eosinophilic leucocytes* of Ehrlich have a lobated nucleus, and their protoplasm contains large granules that color well with acid aniline colors, especially eosin; they develop from the bone marrow. The

most numerous leucocytes are those which may be called *polynuclear*, for the reason that most frequently the nucleus is divided into several parts by extremely fine divisions; they develop in the blood at the expense of small cells furnished by different organs (Ouskof).

The leucocytes all emit protoplasmic appendages that permit them to move about, but they do not all of them possess the power of englobing foreign bodies, that is to say, of playing the rôle of the phagocyte. This property belongs only to the mononuclear and neutrophilic cells, and permits them to englobe the bacteria with which they may find themselves in contact. These bacteria are not infrequently englobed in the living condition. It is in this way that bacilli of anthrax contained in the leucocytes of a pigeon may be seen to push their way out, if the leucocytes be introduced into fluids that are hurtful to their vitality. But the leucocytes do not englobe all the bacteria with which they come in contact, they exercise a choice. In man, for example, the polynuclear leucocytes englobe the streptococcus of erysipelas and the gonococcus that are not absorbed by the mononuclear leucocytes. So, too, when an animal is very susceptible to a bacterium, its leucocytes do not englobe this bacterium.

These differences of sensibility belong to what Leber has called the *chemotactic sensibility*. In producing a keratitis in rabbits with a body extracted from the staphylococcus aureus, this author saw the leucocytes attracted from a distance towards the point of inoculation, and by an ingenious arrangement he was able to compel them to travel against the force of gravity. It is evidently a sort of chemical attraction demonstrated by Massart and Bordet, who saw the leucocytes of the frog attracted in great numbers by the culture fluids from different bacteria, principally the staphylococcus pyogenes albus. The same properties have been observed by many experimenters in the leucocytes of warm-blooded animals, and it is possible to look upon the chemotactic property as a general one. The leucocytes are attracted a long distance by reason of this property, and their tactile sensibility enables them to englobe the bacteria, which are then attacked by the digestive fluids and disappear. It is thus that the anthrax bacilli in the leucocytes of the frog can at first be stained with vesuvin, and then lose their affinity for the coloring matter; now only the membrane of the cell can be seen, and finally this disappears in its turn. Sometimes when these leucocytes cannot kill the bacteria they prevent their development, and when they contain spores, as for example the spores of anthrax, these may retain their vitality, but cannot grow in the protoplasm of the leucocyte. But if there is an inoculation of bacteria endowed with an unusual degree of virulence, the leucocytes do not move towards them, and there occurs

a "negative chemotaxis." In the presence of such bacteria the leucocytes remain in the vessels, and do not exercise their protective properties.

This theory of phagocytosis can be applied to the explanation of immunity as follows: The leucocytes (and probably other cells of the mesoderm, such as those of the endothelium of the vessels) are, in an animal accustomed to the virus, or that has been through a primary infection, accustomed to the toxins secreted by the bacteria in question; if then a new infection takes place, the leucocytes are attracted in great numbers by a positive chemotaxis, and englobe the bacteria before they have had time to produce sufficient toxins to injure the tissues in which they are growing; the chemotaxis is always positive in an animal naturally or artificially immune. Furthermore, the cells transmit their properties to a series of generations, the time during which these properties may be transmitted varying with the bacterium, the intensity of the primary infection, and the individual idiosyncrasy. In fact, immunity, according to the theory of phagocytosis, is simply the accustoming of the leucocytes to the toxins.

A typical experiment in favor of the theory is as follows: Given a normal rabbit, and also one immunized against the bacillus pyocyaneus, if the two animals be inoculated at the same time and with the same amount of this bacillus, it will be seen that in the imumne animal the leucocytes at once assemble in very large numbers, while in the susceptible animal they do not make their appearance at all. The fact of this experiment is indisputable, but it does not seem to be of as much value as has been attached to it, nor to furnish evidence that phagocytosis is constant.

Suppose five immune and five susceptible rabbits be inoculated with the bacillus pyocyaneus, and a drop of the œdematous fluid be taken every quarter of an hour. This drop is diluted with 10 c.c. of distilled water, and then a single drop of the mixture is added to 5 c.c. of gelatin, and plate cultures are at once made. Under these conditions, it is easy to see that the colonies from the susceptible animals before the appearance of any leucocytes are much more abundant and richer in pigment than those from the immune. It is easy, therefore, to see that there occurs in the fluids of the immune animals some modification entirely independent of the presence of the leucocytes.

It follows from this experiment that the theory of phagocytosis cannot explain all the phenomena, so that many observers have put much stress upon the bactericidal power of the blood serum.

Humoral Theory.—Grohmann was the first, in 1884, to demonstrate that if bacteria were sowed in the blood serum their vitality was diminished, and Fodor made the same demonstration. Then came

the works of Nissen, Nuttall, and Flügge, who made plain the degenerations that the bacteria undergo in the blood serum.

It is not possible here to enumerate all that has been done towards proving the bactericidal power of the blood serum, but only to make a very superficial review. It is preferable, therefore, to make a simple *résumé* of the more important memoirs, and then to show how it has been attempted to connect the bactericidal property of the blood serum with the conception of phagocytosis.

Buchner has determined that blood serum exposed to a temperature of 52° to 55° C. loses entirely not only its bactericidal property, but its globulocidal property in contact with corpuscles of another species. It seems probable to him that these two properties are due to the same substance, probably a proteid. If the serum of the dog or the rabbit be diluted with physiological salt solution five or ten times, it hardly, if at all, loses either its globulicidal or its bactericidal properties; but if the salt solution be replaced by distilled water, the serum loses all effect. The serum thus rendered inactive regains its powers if chloride of sodium be added. It follows that the mineral salts play a large part in the bactericidal properties of the serum, without being actually concerned in the production of these properties themselves, as the experiment shows. Repeated experiments showed to Buchner that it is the alkaline salts that seem to have a sort of preservative power in the active substances of the serum, and that they have an analogous action to the red globules; this author also admits that by analogy the active substance is an albuminoid body, complex in its nature, which he calls *alexin;* there may be several alexins.

In 1891 Pane said that it was the alkalinity of the medium that was the cause of the bactericidal power of the serum. Ogata thought he had succeeded in preparing a glycerin extract containing the bactericidal substance of the serum, but his results were contradicted by Petermann.

According to Christmas, the bactericidal influence of the serum itself may be very feeble, while the albuminoid substance in aqueous solution is exceedingly active; otherwise, according to him, the albuminoid substances of the organs in solution behave in the same way. In the two cases there would be perhaps difficulty of assimilation by the bacteria rather than bactericidal power. But Hankin has isolated from the spleen of the rabbit and the rat what he calls defensive globulins. In operating upon animals rendered refractory to anthrax, Christmas was able to obtain a watery extract of albumin, which not only did not furnish a favorable culture medium for the development of the anthrax bacillus, but even, when nu-

trient material was added, actually opposed its development. These experiments are important for the explanation of the occurrence of immunity. Charrin and Roger already determined that the anthrax bacillus developed with difficulty in the inert flesh of mice, and that the serum of the guinea-pig immunized against symptomatic anthrax acquired germicidal properties.

Nevertheless, Sanarelli saw that these bacteria developed well in the serum of vaccinated animals, and even acquired there a greater virulence; in inoculating them, the cellular activity was stimulated, and the leucocytes entered into action with energy to destroy these bacteria. If the bodies were cooled (after the method of Pasteur for rendering chickens susceptible to symptomatic anthrax) the phagocytes were paralyzed, and infection occurred.

These researches bring us again to the theory of phagocytosis. It is the same with those carried on by Lubarsch, Buchner, Nissen, and Hankin, of which the principal results are the following: The destruction of the bacteria is much more active and intense in the serum outside of the body than within the vessels; if the cells be allowed to settle and the blood be defibrinated, the bactericidal property is found in the deposit, and not in the serum; when the leucocytes remain intact outside of the body, the serum is not bactericidal, it becomes so only when the leucocytes are destroyed. From all which is to be concluded that the phagocytes destroy the bacteria by digesting them, and that the feeble bactericidal power of the living serum is the result of the destruction of some of the leucocytes in the body.

Antitoxin Theory.—There remains the theory of the antitoxins, rejuvenating the ancient theory of Chauveau.

Behring and Kitasato, Brieger, Tizzoni and Cattani, Roux and Vaillard, are especially the promoters of this new theory, which thus far seems to be inapplicable to any disease but diphtheria and tetanus.

The following are the principal experiments that tend to demonstrate the presence of an antitoxic substance in the blood of animals vaccinated against, or refractory to tetanus.

When the blood of a mouse, guinea-pig, or rabbit (first immunized against diphtheria or tetanus) is deprived of its cellular elements, the serum immunizes against diphtheria or tetanus; the tetanus toxins may be neutralized either by mixing them with bodies that do not exist in the animals, such as trichloride of iodine, or with cellular products, such as watery extracts of the thymus gland; the mixture of an iodized solution with the tetanus toxins produces an immunizing fluid that injected into animals produces immunity in them; the serum of immunized animals destroys in the test-tube a certain quan-

tity of tetanus toxins; the antitoxin can be isolated in the form of a white powder; this powder loses all action when it is heated to 68° C. for one hour, does not dialyze, is precipitated by absolute alcohol (Tizzoni and Cattani); it is also possible to prepare a preventive and curative serum of diphtheria that will neutralize the diphtheritic toxins.

Applying these results to the explanation of immunity, they lead us to admit that there exists in the blood of animals that have undergone a primary infection or vaccination a substance that destroys or annihilates the bacterial toxins.

This new theory is not unassailable. Behring and Schultz have shown that while the immunity to tetanus persists, the amount of antitoxin in the body diminishes, and that the animal may remain refractory while its blood furnishes no antitoxic serum. On the other hand, it is known that the antitoxic serums confer most often merely a temporary immunity because of the elimination of the antitoxin by the urine.

Finally, Buchner has demonstrated that a prolonged contact of the tetanus toxin with the antitoxin does not destroy the first, and to him it appears that these two substances are not antagonistic except so far as that the latter, the antitoxin, deprives the tissues, the cellular territories, of their receptivity for the toxin, the poison of tetanus. Tizzoni and Cattani admit this interpretation, and think also that the antitoxin of tetanus does not destroy the poison, but preserves the body from its effect.

Theory of Bouchard and Charrin.—As regards the acceptation of these various theories, Bouchard and Charrin are eclectic. The impregnation of the organism by the toxins modifies the constitution; one of the consequences of this modification consists in the formation by the cells of the body of bactericidal elements. When the bacterium penetrates anew into the body, these elements weaken it, it does not produce its entire secretions, or if it does, it does not produce them in the usual quantities; among those that are absent are some that contract the capillaries, and these being absent, the vessels dilate. Therefore the leucocytes pass out freely, the phagocytes collect, and the destruction of the bacteria begins, all the more easily that the number of the latter has been unfavorably influenced by the unfavorable medium in which they have been developing. In an unprotected subject these bactericidal substances do not exist, the bacteria develop unrestrained and produce their different compounds, among them those that prevent the arrival of the defenders (phagocytes).

This theory admits as demonstrated the action of certain toxins on the vasomotors, an action that the experiments of Metchnikoff and

of Sanarelli make only slightly probable; it does not take account of the apparent passage in the blood of substances contained in the leucocytes; it is supported by alleged facts (attenuation of parasites enclosed in sacs permeable to fluids only) whose inexactness is already demonstrated. The French believe that in the actual condition of science, and leaving aside the theory of the antitoxins already combated, Metchnikoff's theory of phagocytosis fits in best with the great majority of facts.

Chauveau's Theory.

Chauveau's theory of immunity is of interest, at any rate historically, and is as follows: He says that he has been occupied for a long time with this important question. The work that has been already done is well known. It is known how he sought to explain the creation of acquired immunity, that it is the resistance of the organism to the infectious bacteria after they have once grown in it, this resistance being the result of the impregnation of the different organic media by the soluble poison or other residual soluble material, the result of the first growth of the bacteria. The demonstration of this mechanism rests upon two principal facts: 1. The aggravation or the attenuation of the effects produced by certain infectious agents, according as they are inoculated in large or small quantities, and thus presented under more or less favorable conditions to overcome the resistance of the organism. 2. The constant appearance of acquired immunity in the young of others inoculated in the last few weeks of gestation with the blood of the spleen, these mothers belonging to a species in which is very seldom observed the passage of bacilli from the blood of the mother to that of the fœtus.

His experiments on the influence of the number of the bacilli were made principally with the virus of anthrax blood of the spleen. He demonstrated that this virus, inoculated in a very strong condition in sheep, that were endowed with a natural immunity or had been rendered more or less refractory by preventive inoculations, has a much greater chance of infecting and destroying these animals when the amount is large, than if it is introduced in a very small quantity. Later, this theory has been strengthened by the result of experiments with two other viruses, those of symptomatic anthrax and of gangrenous septicæmia.

He concluded from these experiments that an infectious bacterium having for a first time multiplied in its culture medium and thus rendered it unfit for a second culture, has produced this result, not by the exhaustion of the soil by taking away from it all the substances necessary for the development of the bacterium, but by leaving in it

hurtful substances, ptomaïns or other soluble substances, that impregnate this culture medium, and make it undergo certain unknown modifications that result in its more or less complete sterilization.

To-day these experiments are not contested (according to Chauveau) and the doctrinal results flowing from them are accepted.

But the experiments on lambs that acquire an immunity in the mother's womb should be spoken of. Chauveau always attached much importance to them, for they furnish a direct demonstration of the mechanism of immunity. The governing idea in these experiments is very simple. In the cases of acquired immunity, the organisms that have become more or less refractory as the result of preventive inoculations have been subjected to the simultaneous action of the living bacteria and of the soluble products that they produce. The idea suggests itself that, if it were possible to confer immunity against anthrax in an organism into which it would be impossible for anything but these soluble products to penetrate, the demonstration of the mechanism of immunity would leave nothing to be desired. Now according to the experiments of Brauell, in pregnant sheep attacked by anthrax the bacilli flourish in the blood of the mother, but do not pass into the blood of the fœtus. The placenta intercepts them, as it does the other formed elements. It is only the soluble materials in the blood that are able to pass through the placenta, invade the fluids, and impregnate the tissues of the fœtus. If, then, these fluids and these tissues become refractory to the development of the anthrax bacilli, it must be admitted that this acquired resistance is due to the action of the soluble materials that are passed from the blood of the mother to that of the young. Experiments have demonstrated that this is so. It has been demonstrated by Chauveau's experiments that the lambs born of mothers inoculated with anthrax during gestation become every one more or less refractory to the action of the anthrax virus. The sought-for direct proof has therefore been found. It is true that its value has been disputed, but this is because the critics have not taken account of the wholly special conditions in which his experiments were made; the author thinks that he may also be a little to blame. As he could not imagine that any one would apply to these experiments the conclusions reached in others made under entirely different conditions, he did not think it necessary to support his own conclusions, that appeared to him to be absolutely unassailable, by giving circumstantial details concerning the manner in which the researches were conducted, and the precautions by which they were surrounded; but the time has come when he thinks a few words must be said upon the subject.

His experiments began in the middle of the year 1879, and were

continued without interruption until the end of the year 1886. The explanation offered by him for the occurrence of acquired immunity was published in 1880 after his first experiments. All the later ones having confirmed these in a most striking manner, he has since 1884 maintained the absolute exactness of the facts published more than four years before, and that prove the establishment of immunity by the action of soluble substances taken by the young from the mother during fœtal life. He reiterated this assertion in 1887, and it now remained for him to demonstrate that the assertion is fully substantiated.

The proofs accumulated during these seven years contain a considerable number of experiments of which at least forty have been concerned with the vaccination of sheep in utero against anthrax. They were made under the following conditions: Those of 1879, 1880, 1881, almost exclusively made upon Algerian pregnant sheep, were confined to the special study for which they were made. The others, dating from 1882 to 1886, might be said to have been made incidentally, being in the course of experiments for an entirely different object. Native sheep were at that time constantly kept in the laboratory for the purpose of studying anthrax virus attenuated by different methods. A good many of these animals were in the last weeks of gestation; they underwent, like the others, the preventive inoculations, often repeated, and always followed by the injection of the strong virus. Some of them died of anthrax, but the larger number escaped and gave birth to perfectly formed young; there were but two abortions recorded.

In order to determine how the lambs born of mothers inoculated in this way acted, it was necessary to study how lambs born under normal conditions behaved. If the young belonged to the native races, it was demonstrated that they were even more susceptible than the adults, and almost all died with unusual rapidity; those coming from Algerian mothers behaved almost as the adults. There were some that succumbed, but these were in a very small minority, much the larger number showed evident traces of disease, and finally there were a few that did not appear to be in the least diseased. But in the latter, as in all the others, infection was manifest by signs that were never wanting; although they might be very slight these were a general sign, the elevation of the temperature, and a local sign, the tumefaction of the lymph glands nearest to the point of inoculation. As the inoculations were always made in the ear by subepidermic or subcutaneous injection, it was always the parotid or prescapular glands that were affected in these experiments.

This is what happened so far as the intra-uterine acquisition of

immunity is concerned. *All* the lambs born of Algerian mothers escaped infection; not one died, not one had any disturbance, not one presented any elevation of temperature or tumefaction of the glands. Most of them, it is true, experienced fleeting disturbances more or less severe; but in this they behaved as did the adults that were subjected to the preventive inoculation, and then to the strong virus.

As stated above, the number of lambs tested in this way was forty at the least; the exact number cannot be given, because the phenomena were so absolutely exact and regular that a complete record was not kept towards the end; it is in fact astonishing that not a single case of death occurred upon the use of the strong virus; the same success does not attend the inoculation of adults which have been vaccinated. There certainly might have been some cases of death among the animals without the importance of the facts being diminished, but this accident did not occur once. Thus we see that all the lambs born of mothers inoculated against anthrax during the last weeks of gestation acquired immunity by the passage of soluble substances manufactured in the blood of the mother and passing into the fœtus. Unquestionably this is so, if it be true that the bacilli do not pass at all, or only exceptionally, into the blood of the fœtus.

Upon beginning the experiments, there seemed to be no doubt that the dictum of Brauell and Davaine was true that the bacilli do not pass through the placenta; this depending upon the fact that the blood of a mother dead of anthrax invariably communicated the disease, while the blood of the fœtus did not. The experiments of Toussaint, in which he succeeded in vaccinating sheep with blood in which he thought he had destroyed all the bacteria by heat were those that attracted attention to this point. Although the results seemed to depend upon the production of a soluble product that acted as a vaccination material, the quantity used was too small to permit them to be explained except upon the supposition of reproduction, and this was only to be obtained as the result of bacterial life. Toussaint persisted, however, until a new objection was offered, that in certain cases there might be *erratic* bacilli which, in the cases in which he used the blood of the fœtus, might have passed through the placenta, and might thus have been active in the production of the resulting immunity. But success never attended the attempt to demonstrate the presence of the bacilli in the blood of the young of sheep dead of anthrax.

Finally, we know of infectious diseases that, in the pregnant sheep, they are transmitted with the greatest ease to the fœtus with all their pathologico-anatomical characteristics—for example, symptomatic anthrax. On the other hand, has any one ever observed the

lesions of ordinary anthrax in the young of mothers (sheep) dead of this disease? So far as Chauveau's experiments are concerned, it was never seen even in cases in which the heart's blood of the fœtus was found to be virulent. It is known that the principal lesion is in the spleen, whence its name, "splenic fever;" on the other hand, in all the numerous experiments that Chauveau made, there was never seen the slightest alteration of the spleen of the fœtus, this organ was absolutely healthy. The same could be said in regard to all the other organs, especially of the lymphatic glands; it is therefore an exaggeration to pretend that the fœtus can contract anthrax in the abdomen of the mother, it does not even contract the rudimentary disease that makes its appearance in the animals subjected to vaccinating experiments, and that are living an independent existence. So that Chauveau was forced to the conclusion that the rare infectious agents that occasionally make the blood of the fœtus virulent are *erratic* bacteria that always come from the mother, and that are not capable, or very slightly so, of multiplying in the young. Indeed, it is not impossible that the latter may have been affected by the vaccinating material received from the other before the multiplication of the bacteria, that is always late, had made sufficient advances to permit the penetration of the placenta.

The conclusion of all this is that the immunity acquired by the lambs in utero is due to the presence of a soluble vaccinal material derived from the mother.

C. Fraenkel and Sobernheim reach the following conclusions: So far as artificial immunity is concerned with respect to artificial laboratory cholera in guinea-pigs, primary immunity, produced by the incorporation of heated fluids of bacterial origin, is caused by the action of certain bacterial proteid substances; it depends on the "reactive" capabilities of the cells of the animal concerned, and makes itself known in the increased germicidal powers of the organism. This changed condition, this peculiar state of "irritabilty" may continue even when the influences thereto, that is to say the bacterial products, have been removed from the body either naturally or by artificial means. In this way may be explained the persistence of immunity even after complete renovation of the blood. The immunity brought about by the introduction of serum into the system depends upon two different processes. In the first place, we have the implantation of certain qualities of bactericidal substances; this is Ehrlich's passive, or Behring's antitoxin immunity. But with the serum there are also introduced other substances which act as specific stimulants to the cells, causing the latter to produce substances

possessing immunizing virtues. The immunity of serum origin is thus both active and passive.

Buchner says that in connection with the exact causes of immunity the great difference between natural and acquired immunity has been definitely established. Natural immunity seems to be brought about by the bactericidal action of a protective substance or alexin in the blood serum. This alexin differs from the antitoxin found in the serum of animals artificially made immune. Alexin acts upon the bacteria and also upon the red cells and even leucocytes belonging to animals of other species, while such bactericidal and globulicidal action is not possessed by antitoxin. Alexin is most easily decomposed, whereas antitoxin is a stable body. The effects of antitoxin are the same, whether coming from one animal or another, and only depend upon the degree of acquired immunity possessed by the animal. The author contends that the serum of animals made immune contains both alexin and antitoxin. Thus a body can be extracted from the serum of an animal made immune and can be transferred to another. There are two explanations with regard to this body, namely, that it is a reactive product on the part of the tissues, or that it is a modified product of the bacterial cell. The chief point, however, is that the living body is necessary for the production of this antagonism of the antitoxin against the disease. The author would limit the term immunity to the acquired form, and thus speak of specific immunity, including the immunity against the bacterial poison, and of natural resistance. The action of tuberculin does not lie in producing any specific immunity, but in conferring an increased natural resistance. In this respect, Buchner refers to the researches of Hueppe in relation to cholera, and those of Fraenkel and Rumpf in relation to the treatment of enteric fever by killed cultures. The author maintains that efforts are being made in the direction of protection against disease by increasing the natural resistance. He then quotes an experiment in which sterilized wheaten gum was introduced into the peritoneal cavity of a large rabbit. After it was killed, the gum was found filled with leucocytes, and possessed of marked bactericidal powers against the bacillus coli communis. The leucocytes were destroyed by freezing, and yet the bactericidal powers remained. These powers were soon destroyed by heat. The author would attribute these powers to the presence of alexin, probably derived from the leucocytes. He looks upon the blood as the great antiseptic and disinfectant of the body, and draws attention to the importance of the study of this fluid in diseased conditions.

The Defensive Proteids.

The following is the summary of Gamaleïa concerning the defensive proteids: If scientific evolution consists in replacing confused and complex ideas by simple and precise ones, this theory of immunity forms a real progress. For the somewhat mystical hypotheses of the capricious activity of the leucocytes and the reactive power of the tissues, which tend to take possession of experimental pathology, it substitutes the extremely simple theory that immunity is due to antisepsis, and that the bacteria are destroyed in the animal body by easily isolated disinfecting substances acting in the chemist's glass as in the animal economy, in a word belonging to a class of bodies already well understood, the germicides.

It is a long time since the idea that immunity might be due to a "preventive" substance entered the minds of experimenters. Pasteur, Chauveau, and Klebs published theories with this for a basis, but it was difficult to demonstrate this "preventive" substance. The first experiments (Grawitz, Gamaleïa) were negative. But Grohmann, in 1884, demonstrated that fresh serum exercised an attenuating influence upon anthrax bacilli. Fodor found that fresh blood destroyed this bacterium. Nuttall demonstrated that organic fluids like serum, the aqueous humor of the eye, and the serous fluid of the pericardium, really possessed the power of destroying bacteria, and that this antiseptic action is destroyed in them by raising to a temperature of about 50° C., or over. Buchner's researches showed the nature of this antiseptic action. He demonstrated that it was contained entirely in the serum, and that the corpuscles in being destroyed in defibrinated blood may more or less mask and destroy the bactericidal action of the serum. He demonstrated also that by repeated freezing of the serum, it may be separated in several layers of which the lowest is the most active; and further, that the bactericidal action of the serum is destroyed if it be diluted with distilled water, or if it be dialyzed against it.

The bactericidal action of the serum is not hindered if one uses saline water in these last two cases, instead of distilled water, and it appears from these results that the bactericidal action is brought out only in saline solutions; this would ally the bactericidal substance to the globulins, which are held in solution only in saline fluids.

After Buchner, the most important researches have been made by Ogata and Iasuhara, and Behring and Kitasato, who demonstrated the extremely important part played by the fluids of the body in the acquirement of immunity.

According to the work of these observers, and of others to whom we shall have occasion to refer later, immunity is due to the presence of albuminoid substances that may be called, following Hankin, *defensive proteids*, which have the power of killing pathogenic bacteria, of attenuating them, and of destroying their toxic products. We shall pass rapidly in review the properties of these defensive proteids.

Bactericidal Proteids.—Animals have in their serum and other fluids substances endowed with very considerable bactericidal powers. A well-studied example of these bactericidal proteids has been found in the serum of white rats. These animals are, as is well known, refractory to anthrax. Behring, in studying the causes of this immunity, discovered that their blood serum did not permit the bacilli to grow, and even destroyed them. He endeavored to measure this germicidal power by comparing it with well-known antiseptics like sublimate and carbolic acid. He found that one part of fresh serum of the white rat added to eleven to fifteen parts of the serum of sheep (which is not antiseptic to anthrax) would prevent the growth of the bacilli in the latter; 2.5 c.c. rat's serum mixed with an equal part of sheep's serum would completely destroy in twenty-four hours the bacilli coming from the blood of a guinea-pig affected with anthrax. To obtain the same preventive and sterilizing action in sheep's serum with sublimate and carbolic acid, it was necessary to use the first in the proportion of 1:1,000, and the second of 2:100.

To appreciate in all their value these figures, they must be considered in connection with another property common to all the antiseptics, namely, their toxicity to animals (Bouchard, Behring). While sublimate and carbolic acid kill the animal in doses five to seven times smaller than would be necessary to prevent the development of the bacteria in their serum, and are therefore not fit for internal antisepsis, the bactericidal proteids are present in sufficient quantities for disinfection of the rat's serum, in a condition of health. It is just here that the most valuable property of the defensive proteids comes in, that of being the least toxic of all substances known as antiseptics, which makes it possible to employ them for internal antisepsis, that is to say, for the prophylaxis and treatment of the infectious diseases.

Behring studied also the chemical properties of rat's serum, and demonstrated that it surpasses all others in the degree of its alkalinity. He was inclined to put the bactericidal power in relation with this alkalinity, and to believe that the antiseptic action was due to an organic alkali, which was extremely active, and still unknown, a leucomaïn (A. Gautier).

Since then, Buchner has demonstrated that the antiseptic action

of animals is limited very closely to albuminoid bodies. Nevertheless, these two opinions are not necessarily opposed, and recently Hankin has endeavored to reconcile them. In fact, there are already known albuminoid bodies that have a reaction that is alkaline, due perhaps to the combination of an albuminoid with a ptomaïn. All these bodies are albumoses, that is to say, albuminoid bodies, soluble in water or in dilute saline solutions, precipitable by alcohol and supersaturated sulphate of ammonia, non-precipitable by heat. Further, Hankin endeavored to isolate the albumose from the spleen of the rat, and found that this albumose had an alkaline reaction, and, on the other hand, possessed the power of destroying the anthrax bacillus. He also succeeded in curing anthrax in guinea-pigs by means of this albumose.

Nevertheless, in studying more closely animal antisepsis, certain observers (Nuttall, Lubarsch) soon ran against an apparent contradiction upon which much stress has been laid by the partisans of the older theories of immunity. This apparent contradiction lay in the fact that the bactericidal power of the animal serum did not in all cases correspond to the natural immunity of the animal furnishing the serum. So that, on the one hand, the serum of the frog, rat, and pigeon, refractory to anthrax, had a marked bactericidal action on the bacillus of anthrax, while the serum of the dog had but a very slight action in this direction, although the dog is also refractory to anthrax. The serum of the rabbit, on the other hand, has a very marked bactericidal action on anthrax, although the rabbit is extremely susceptible to the disease. But the close analysis of these facts soon demonstrated that they do not constitute a fundamental objection to the theory of the defensive proteids.

In the first place, if the serums of similar species of animals are compared as they are or are not immunized against an infectious disease under investigation, it is found in general that the immunized animals have a more bactericidal serum than one that is not immunized. For example, rabbits immunized against anthrax have a more bactericidal serum than normal rabbits (Lubarsch).

Secondly, it has been found that animals naturally immune to anthrax, whose serum is not sufficiently bactericidal to the bacilli, and such is the case in the chicken and the dog, react to anthrax infection by a fever; and it is now known that this fever is due to the production of defensive proteids (Gamaleïa, Hankin).

Further, it has been proved that, in the case of animals with an extremely bactericidal serum which are yet susceptible to infection, as is the case with rabbits and anthrax, there is at the beginning of the infection an active destruction of the bacteria, and this action

ceases only when the defensive proteids have been exhausted. (The first observation was made by Fodor, the second by Flügge and Gamaleïa.)

But, to be complete, the analysis of the facts must take into consideration other defensive proteids than those that destroy bacteria. For it will be seen very soon that the dog, whose serum is poor in bactericidal proteids and which yet is insusceptible to anthrax, has a serum that is rich in attenuating proteids with respect to the anthrax bacillus. Therefore the dog, infected with anthrax, commences by making the bacteria harmless, then acquires by its febrile reaction the bactericidal proteids, and destroys the attenuated bacterium.

Attenuating Proteids.—It is Grohmann also who first discovered the attenuating action of fresh serum on the anthrax bacillus. Since then this attenuating action has been observed by many others, and has been especially studied in the case of the anthrax bacillus.

The most complete work is that of Iasuhara and Ogata. Relying upon the numerous experiments of different authors (Oelmer, Kitt, Petruschky, Emmerich and Di Mattei, Lubarsch, Finger, Gamaleïa, Pouquiet, and others) who have demonstrated that refractory animals possess certain properties that attenuate the bacteria that are inoculated, Ogata and Iasuhara have endeavored to determine if this attenuating property resides in the serum of the immune animals. They inoculated anthrax bacilli in the fresh serum of the frog, the rat, the dog, and the rabbit, and found that while the cultures which came from the serum of the rabbit remained virulent for the mouse, the remaining cultures coming from the serum of immune animals were attenuated, and could not convey anthrax to mice.

This attenuating action of the serum of immune animals explains easily their immunity; but the authors went further, and queried if this attenuating action of the serum, which is exerted in the body of immune animals and also in the test-tube, cannot persist also in the bodies of other animals that are not immune to anthrax. To solve this problem, they injected the serum of the frog and the dog into mice and guinea-pigs inoculated with anthrax. Thus a drop of the serum of the frog, and one-half to one-fourth of a drop of the serum of the dog preserved mice from a dose of anthrax which killed mice not treated. For guinea-pigs it was necessary to employ 2 c.c., for rabbits 4 and 8 c.c. to preserve them from anthrax.

These results of Ogata and Iasuhara on the attenuating proteids have since been confirmed, for anthrax (Behring, Hankin), and for other different diseases. Thus, for example, in Bouchard's laboratory, H. Roger has found that the streptococcus of erysipelas grows very freely in the serum of animals vaccinated against this disease,

but that it becomes attenuated, and that its attenuation is more marked the more intense the immunity of the rabbit from which the serum came. On the other hand, Metchnikoff for the pigeon and the white rat, and Malm for dogs, have endeavored to show that these animals, which are refractory to anthrax, instead of attenuating the anthrax bacilli, increase their vitality. But they committed the error of not inoculating the bacilli that come from refractory animals; they made first a culture in bouillon, and it is well known, from the experiments of Toussaint and Chauveau, that bacteria deprived of virulence, by heat for example, become virulent in young cultures. So, also, Metchnikoff isolated a bacterium contained in the leucocyte of a pigeon. To prove that it was virulent, it should have been inoculated in a guinea-pig, for it is known (Watson Cheyne) that a single bacillus is all that is necessary to infect a guinea-pig; but this the author could not do, and therefore his assertion that the bacillus was virulent was not well founded. Then, too, the experiments establishing the attenuating power of the serum of immune animals are already very numerous, and it is possible to consider as settled that the serum of immune animals contains attenuating substances. But it will be seen that the rôle of the defensive proteids is not limited to bactericidal and attenuating action, there are others that have an antitoxic effect.

Antitoxic Proteids.—Behring and Kitasato first demonstrated in 1890 that the blood and the serum of rabbits vaccinated against tetanus had the power of destroying in the test-tube the toxin of tetanus. Following is one of their experiments: One centimetre of a filtered tetanus culture, sufficiently powerful to kill a mouse in several days when injected in a dose of 0.00005 c.c. (cinq cent-millièmes) was mixed with 5 c.c. of serum of a rabbit refractory to tetanus. Twenty-four hours afterwards four mice were inoculated with 2 c.c. of this mixture each, containing 0.033 c.c. of the original filtered culture. The same filtered culture not mixed with the antitoxin was injected into control mice in a dose of 0.0001 c.c. These died in thirty-six hours, while the first four remained immune and unharmed for an indefinite period. This antitoxic action of the serum of immunized rabbits was exerted not only in vitro, but in the bodies of mice that are usually so susceptible to anthrax. Thus, for example, 2 c.c. of the serum of immune rabbits was enough to vaccinate mice against tetanus. The experimenters even succeeded in saving animals in which the disease had already made its appearance, tetanic convulsions being already present, by the use of rabbits' serum.

The same observations have been made by these authors with regard to diphtheria, in which it was found that the serum of animals

immunized against this disease had the power to destroy the diphtheritic poison.

Tizzoni and Cattani have been able to confirm the results of Behring and Kitasato so far as regards tetanus. Some observers have endeavored to upset the results of Behring and Kitasato, by quoting those of others (Gamaleïa and Charrin) who have shown that animals may be immunized against certain diseases, at the same time remaining susceptible to the toxins of these diseases. But in these cases (vibrionic disease, pyocyanic disease, cholera) it is shown that the animals defend themselves by the bactericidal proteids which they possess in much greater quantity than the unimmunized (Behring and Nissen, Charrin and Roger, Zasslein) and not by the antitoxic proteid. It can be seen by the rapid analysis here given of the disinfecting power of the animal, the great number of facts the advocates of this doctrine can adduce in its favor. But as it only dates from yesterday, a great number of fundamental questions are still undecided. Thus the precise nature of the defensive proteid is not yet fully made out. It is an alkaline albumose according to Hankin, a special condition of the serum globulin according to Buchner, diastase according to other authors.

The distribution of the defensive proteids in the various tissues of the body is not yet known. Hitherto, the fluids of the body have been especially studied, the serum of the blood, the aqueous humor, the serous fluid of the pericardium; but it is known that certain organs of the body contain proteids, such as the spleen (Hankin, Gamaleïa) and the muscles (Fria).

To this latter question is attached another of extreme importance, namely, as regards the place where the defensive proteids are formed. Probably the different organs are charged with the duty of furnishing to the body the different defensive proteids, like the liver, the muscles, etc., but these questions have not yet been settled by experimentation, for even in normal physiology the knowledge of the internal secretions of the glands is but beginning to be understood, revealed by the experiments of Minkowsky on the pancreas, of Schiff, of Brown-Séquard, and others.

In spite of the great number of unknown points that still surround the theory of the defensive proteids, and the immunity produced by them, it is possible to predict that it will emerge victorious from the struggle against the old prejudices that surround this branch of general pathology, and the numerous hypotheses that have already been formed. It will be victorious, because it has already given certain proofs of its importance in immunizing and curing animals by means of these defensive proteids.

Artificial Immunity by Means of the Defensive Proteids.

If the refractory condition of the animal enjoying immunity, either natural or acquired, is due to the presence in the body of an antiseptic substance that can be isolated from the living body, nothing is more natural than to attempt to produce by this antiseptic substance in the living body immunity in animals not endowed with it.

The first to do this successfully were Hericourt and Richet, who showed that the peritoneal transfusion of the blood of the dog (immune to staphylococcus septicæmia) in rabbits, ordinarily susceptible to infection with this coccus, renders the rabbits immune to it. The authors, however, used the whole blood for their experiments, which makes it impossible to consider their work as a decisive proof of vaccination by means of defensive substances contained in the fluids of the animal.

The first to confer immunity by the serum were Ogata and Iasuhara, whose experiments upon anthrax have already been spoken of. They also obtained similar results with septicæmia of mice. In reference to anthrax, the experiments of Behring must also be mentioned, who immunized mice with the serum of the rat; and those of Hankin who was able to immunize mice by means of the serum of the rat, and by the use of an albumose extracted from the spleen of the rat.

Behring and Kitasato produced immunity against tetanus, and even cured the disease by means of vaccinated rabbits. They obtained the same results in diphtheria. Emmerich cured rouget by the use of the serum of vaccinated rabbits. Hericourt and Richet enhanced the resistance of rabbits to avian tuberculosis by infusing in them the serum of dogs. Bouchard obtained the same effects by this same infusion so far as concerns the resistance of the rabbit to the pyocyanic disease. Other identical results are reported in enormous numbers.

The importance of these experiments is very great. From the theoretical point of view, they completely cover the question of the nature of immunity. For, unless one ventures upon unlikely and artificial explanations, it must be acknowledged that the serum that confers immunity does it by the same antiseptic properties, defensive proteids, that have been determined in the bodies of refractory animals, and also in the test-tube. It must be admitted, therefore, that the serum that confers immunity is sufficient also to explain it, and that there is no need to have recourse to other hypotheses that have nothing to recommend them except "*post hoc, ergo propter hoc.*"

From the practical point of view, these experiments give us for the first time a rational method, since it is founded upon internal antisepsis (Bouchard), of preventing the infectious diseases and of curing them.

We conclude, then, that actually the only plausible theory of immunity is that which explains it by the disinfecting properties of the humors, by the special antisepsis of the animal, by the defensive proteids. Any complete explanation must take into account the three properties of these defensive proteids, their bactericidal, attenuating, and antitoxic action.

SERUM TREATMENT.

Our practical application of the knowledge gained in regard to the production of artificial immunity is generally sought to-day in the direction of serum therapeutics, or orrhotherapy. It has been attempted to secure artificial immunity by the use of the actual cultures of the bacteria, modified in various ways; by extracts of the cultures; by extracts of the bacteria, etc.; but the most successful results outside of the laboratory have been obtained in the case of diphtheria, and this success has been secured as the result of effort in a different direction from any of the preceding, that is, by the use of the serum of animals artificially rendered immune to the disease. This procedure, which has been so successful in its application to the cure and prevention of diphtheria, did not reach its present stage until after many most elaborate and painstaking studies of the blood serum in its effects upon bacteria and animals had been concluded.

Our present knowledge of the properties of the blood serum is well summarized by Achalme, whose book presents the subject in a very clear and concise way, and from which we shall quote freely in the remainder of this article.

General Properties of Serum.

It is claimed by the French that Richet and Hericourt were the first who applied the actual principle of serum therapeutics which they formulated in their work on the micrococcus pyosepticus. After them many observations, principally due to Behring's initiative, demonstrated that the blood serum could not be considered, as heretofore, a simple inert vehicle, but, on the contrary, that it appeared to be endued with properties that might be called vital, to which could be attributed a part of the resistance of the individual to exter-

nal causes. This discovery coming at the moment when the still recent theory of phagocytosis was being actively combated, especially in Germany, opened a new line of argument for its numerous opponents, and although they did not succeed in refuting the conclusions of Metchnikoff, their studies were productive of valuable results.

It was very quickly determined that the blood serum exercised, either directly on bacteria, or indirectly in the economy of the animals into which it was injected, certain influences until then unknown, but the practical application of which was not long delayed. The principal facts necessary for a proper understanding of the phenomena of serum therapeutics are the following:

Bactericidal Power of the Serum.—The bactericidal properties of the blood serum must be placed first in chronological order, as having been especially demonstrated by Behring with the serum of the rat attacked with anthrax.

From 1888, the time of his first researches, until 1892, when he discovered the antitoxic power of the blood, many experiments were published, especially in Germany, attempting to make this bactericidal action of the serum play an important part in the production of immunity. From this work the interesting fact stands out, whatever the explanation may be, that the serum of certain animals not only hinders the development of certain species of bacteria, but also appears to destroy them, so that at the end of about twenty hours no vitality can be demonstrated by means of cultures; but this fact alone is very far from having a general application to immunity, for although certain coincidences may have been noted between the refractory condition of an animal and the bactericidal property of its serum, the divergences observed are numerous. This absence of uniformity appears to demonstrate clearly that the rôle of the bactericidal properties of the serum is not of practical importance in the resistance of the organism. Some observers have gone even further, and are unwilling to admit that the bactericidal power is a biological property of the serum, considering it as a simple accident, according to some due to the presence of carbonic acid, according to others to the simple phenomena of osmosis by which is produced a sudden transportation of the bacteria from one medium to another. Certain facts indeed support this latter view. Direct experimentation demonstrates that bacteria, less sensible perhaps than infusoria, support no less poorly these changes of medium, and thus, basing the assertion on the facts, we can attribute a bactericidal property to egg albumen, and even to distilled water. It is also possible to allege the ready accustoming of the bacteria to this medium of culture, which appears at first so hurtful to them; for in fact, if we wait two or three days,

there is finally obtained a development of the bacteria in the substituted bactericidal serum. In spite of these and other arguments, it is difficult to regard as a simple physical phenomenon the biological power of the blood. It would be hardly admitted that the osmotic power of the serum of the vaccinated guinea-pig differs in any sensible degree from that of the serum of a normal guinea-pig. The instability of the bactericidal power is also a good argument in favor of its biological nature, if not of its vital nature. It is in fact destroyed by heating to 55° or 60° C., while none of the other physical or chemical properties of the serum seem to be in the least degree modified. Because of these phenomena, it was perfectly natural that attempts should be made to isolate a substance to which might be attributed the hurtful action of the serum upon the bacteria; but these researches were negative, for control experiments did not verify the existence of the proteids, globulins (defensive), or alexins, of Hankin and of Buchner, nor that of the bactericidal diastases of Ogata and Iasuhara. The nature of this bactericidal property is so little determined that it is impossible not to compare it to the globulicidal properties which will be mentioned later. Its existence, however, has established the fact that the blood serum cannot be looked upon as an inert material, and has served as the point of departure for important discoveries in serum therapeutics.

The Attenuating Power of the Serum.—The most flagrant contradictions of the bactericidal phenomena lose much of their importance from the point of view of the genesis of immunity. Some authors, nevertheless, seek to reconcile observed facts with theory, and it is from this that the conception of the attenuating power of the fluids had its rise, due principally to the works of the followers of Bouchard, and especially of Roger and Charrin. According to them, even if the bacterium is not always deprived of its vitality by the action of the fluids of the refractory animals, it nevertheless is markedly influenced in its most important property, from a pathogenic point of view, that is to say, its virulence. These authors seem to demonstrate that the bacillus pyocyaneus does not secrete its coloring matter in the fluids of immune animals, that the inoculation of cultures of the pneumococcus or of the streptococcus in the serum of animals protected against the affections produced by these bacteria is harmless, in spite of the development of the bacterium, which development, so far as the streptococcus is concerned, is more abundant than in the serum of non-vaccinated animals. It is not possible to review the contradictory results obtained by various authors who have attempted to repeat these experiments. The conclusions appear to be that this apparent attenuating property has been confounded

with the protective power of the serum. In the experiments of the authors spoken of, this factor, at that time unknown, was for that very reason entirely neglected; and the mixture of serum and bacteria was found harmless, not because the bacteria were attenuated by the action of the serum, but because the serum preserved the living tissues against the pathogenic action of the bacteria which accompanied it. From the later work on this question, it appears, on the contrary, that in the blood of refractory animals, whether in the living organism or in the test tube, the virulent properties of the bacteria are increased, and that this increase is the result of a new adaptation or of a selection among the most resisting bacteria; so that to-day the existence of an attenuating property is more than doubtful.

The Antitoxic Power of the Serum.—In following out his studies upon the bactericidal action of the blood, Behring very soon found himself blocked in his conclusions by the fact, easy of demonstration, of the development and persistence of the bacterium at the point of inoculation in refractory animals. The question at once arose, whether, instead of acting upon the bacterium itself, the fluids did not exert their influence upon the products of secretion by neutralizing or destroying them. From this conception arose the great discovery of the antitoxic power of the fluids, and especially of the blood serum. Behring and Kitasato found that it was sufficient to mix the toxins of tetanus or diphtheria with small quantities of the serum of an animal vaccinated against these diseases to be able to inject the toxins into susceptible animals without harm. The result was the same if the mixture was made in the body of the animal instead of in the test tube; in fact, these observers demonstrated that the injection of serum at another point, and at a time a little before or a little later than the injection of the toxin, could protect the animal against many times the ordinarily fatal dose of the bacterial poison. This discovery was a revolution, and it was believed that it would deal a deathblow to the theory of phagocytosis. The explanation which first presented itself for this phenomenon of neutralization of the effects of the toxin was a very simple one, namely, that the serum acted directly upon the microbic poison and destroyed it, or at least transformed it into an inoffensive substance. This power appears to be less destructible than the bactericidal property, of which it is entirely independent, although Buchner does not think so. Heating to 65° C. for twenty-five minutes does not destroy it. It also withstands the dilution of the serum in distilled water, and even the addition of certain antiseptics, such as carbolic acid and formaldehyde. It was perfectly natural to attribute this remarkable property to the presence in the blood

of a special body to the existence of which the antitoxic power could be attributed.

The name of antitoxin has been given to this body, and it has been successively compared to a globulin or a diastase; whatever it may be, its power surpasses the imagination, since in the condition of dilution in which it is found in the serum, it is sufficient to neutralize enormous doses of toxin. In such a matter nothing can be more eloquent than figures. One cubic centimetre of the serum of a horse vaccinated by Roux and Vaillard against tetanus was sufficient to neutralize in the test tube thirty times its volume of toxin; it was possible then by the addition of .0001 c.c. to neutralize completely the hurtful action of an otherwise fatal dose. To preserve mice, the necessary quantity is so infinitely small that it is difficult to give an exact notion of it. Serum of an activity of one-millionth and more has been obtained, the unit of measurement being the quantity necessary to immunize a gram of mouse; thus a cubic centimetre is sufficient to protect 1,000 kgm. of mice or more, that is to say, almost seventy thousand of these animals, each one weighing about 15 gm., against a fatal dose of toxin.

The discovery of such power, it will be easily understood, gave rise to therapeutic hopes, which, if they have not been completely recognized in tetanus, have been surpassed in diphtheria. The practical deductions that have come from the researches of Behring and Kitasato have, so to speak, popularized their theoretical idea of the destruction of the toxin by immunizing serum, emphasizing thus the existence of the antitoxic property of the blood; nevertheless, upon better analysis of the phenomena, and especially upon attempting to extend this notion to other affections less visibly toxic than tetanus and diphtheria, it is very quickly apparent that it is, to say the least, incomplete.

Immunizing Power of the Serum.—Metchnikoff, in certain researches upon the blood of rabbits inoculated against hog cholera, determined that the serum of these animals exerted a preventive and curative action in fresh animals, without at the same time possessing any bactericidal, attenuating, or even antitoxic property. This new idea opened a fresh vista. It was seen that a false direction had been taken in attempting to determine the direct influence of the serum on the bacterium or the toxin, and that one of the most important factors of the experimentation had been neglected, that is to say, the organism of the inoculated animal; whether inoculation was made with a mixture of serum and bacteria or a mixture of serum and toxin, instead of acting upon these elements by neutralizing their hurtful action, it appeared that the serum exerted its influence upon the

economy of the animal by increasing the activity of its means of defence. It was this idea that Metchnikoff put forward, and that he has supported by what appeared to be irrefutable facts. According to him, the action of the serum is especially a stimulation of the organic resistance, and is exerted especially upon the phagocytes that it makes more competent to fulfil their defensive rôle. Many facts can be brought forward to support this seductive theory.

Globulicidal Property of the Serum.—This, which is very like the bactericidal property, has been especially studied by Daremberg in France, and Buchner in Germany. These observers found that when they introduced the blood globules of one animal into the serum coming from another, the corpuscles were rapidly deformed and completely dissolved in the course of a few moments, and this phenomenon occurred as well in the circulating blood of an animal as in the test tube. Buchner attempted to identify this method of action with the bactericidal power of the serum, and his hypothesis appears to be quite probable, for besides the fact that the two are very much alike, subjection to a temperature of 55° C., exposure to light, or a change in the saline constituents, destroyed the two properties more or less rapidly. The existence of a special albuminoid material, or an alexin as Buchner calls it, in which this globulicidal power resides, appears as doubtful as does the existence of the defensive proteids of which we have spoken in connection with the bactericidal power of the serum.

The Coagulating Power of the Serum.—If there be introduced directly into the veins of an animal serum coming from another species, it may produce an intravascular coagulation as a result of the precipitation of the fibrin. In their experiments upon the treatment with the serum of the dog of the infection produced in the rabbit by the staphylococcus pyosepticus, Richet and Hericourt discovered this fact, but found that it can be avoided by making the injection not directly into the blood current, but into the cellular tissue, or in a serous cavity, so that the absorbed serum could arrive in the blood only through the lymphatic system. Hayem has also shown that, similarly to the globulicidal power, the coagulating property disappeared under the influence of heating to 55°, which appeared to show that it was due to a coagulating ferment; and these facts were also confirmed by Mairet and Bosc, who lowered the temperature at which the serum loses its coagulating properties to 52°, and in this way differentiated it from the toxic property.

The Toxic Power of the Serum.—As a result of their researches these two authors found that, in addition to the accidents which are the results of the coagulation of the blood, the injection of the serum

of a different species may produce actual symptoms of intoxication, made manifest by myoses, temperature changes, interference with respiration, and even fatal convulsions. These toxic properties, which they attributed to the presence of albuminous materials, are somewhat more resisting than the coagulating power. They disappear only after heating to 57°, and resist the addition of chloride or sulphate of sodium. These toxic properties vary very much in different species of animals; thus, according to the researches of Mairet and Bosc, the serum of man is much more toxic and less coagulant than the serum of the dog. This toxicity of the serum also varies greatly according to the health or illness of the animal that furnishes it. Quinquaud insisted upon the toxicity of the blood in certain cutaneous affections, and Stern emphasized the extreme toxicity of the blood in the course of erysipelas. A matter of great importance is the difference in the hurtful action of the serum according as it is injected into the subcutaneous tissue or directly introduced into the veins, and, of course, this latter method should always be avoided in the therapeutic use of serum.

The existence of these various properties confirms what has already been said of the vital nature of the serum, which was formerly considered to be an inert substance. These properties may also be compared to other chemical phenomena due to the direct action of the blood, that have been investigated of late years; it is to enzymes, so to speak, living, that is attributed the glycolytic property of the blood, a property to which is due the disappearance of a part of the sugar contained in the blood, whether it be in circulation or in the test tube. The pepto-saccharifiant power, characterized by the production of sugar at the expense of peptone, is a phenomenon of the same character.

Serum Treatment in the Experimental Diseases.

Septicæmia Produced by the Staphylococcus Pyosepticus.

Richet and Hericourt, in 1888, gave the results of their experiments to the Academy of Science. The bacterium of which they made use came from a non-ulcerated epithelial tumor of a dog, and was extremely virulent to rabbits, which it killed, producing enormous purulent collections, and a rapid septicæmia, in which characteristic it resembled the staphylococcus albus. They found that the dog was absolutely refractory to the action of this bacterium, and the interest of their communication came from the new application which they made of this property. They were able to protect rabbits

against this fatal septicæmia, not only by vaccinating them with old cultures, but by injecting into the peritoneum the blood of the dog, a refractory animal. In a second communication they again laid stress upon this fact of the protection of a sensitive animal by the blood of an immune animal, and added that this protection was still more efficacious when they employed the blood of dogs, whose natural immunity had been reinforced by the inoculations of the bacterium. It was this second assertion which was the most important, and which made serum therapy take the decisive step that has made it the object of the attention of all; and the French, therefore, claim that the honor of founding this method of treatment should be accorded to Richet and Hericourt.

Anthrax.

Experiments upon this disease have been much less conclusive. Behring demonstrated the bactericidal properties of the blood of the white rat, an animal that had been looked upon as refractory to anthrax. Wishing to determine whether this property could be active as well in another animal as in the test tube, he injected anthrax spores mixed with the serum of the rat into mice, and saw that under these conditions the mice suffered no ill effects. Hankin, Ogata, and Iasuhara repeated the experiments and arrived at analogous results, for naturally they considered that there was a connection between this bactericidal power and the immunity of the white rat on the one hand, and the preservative property on the other. They attempted to isolate the substance which appeared to them to be the cause of these phenomena. Behring, arguing from the fact of the strong alkalinity of the blood of the rat, attributed it to the presence of an animal alkaloid, a ptomaïn. Hankin thought he saw the action of certain albuminoid substances, which he called alexins, or defensive proteids, and Ogata and Iasuhara thought they had isolated a diastase that possessed the same properties. Metchnikoff and Roux determined that this protective action of the serum of the rat occurred only on condition that there was actual contact of the bacteria or their spores with the fluids extracted from the rat. When the bacterium and the serum were injected separately, even if the injections were made at a point very near each other, the preservative effect was absent. Metchnikoff and Roux, in attempting to establish the connection existing between the preservative power of the serum and the immunity attributed to white rats, reached results absolutely opposed to those of Behring, of Franck, and of others who considered these animals refractory to anthrax. They found that most of the white rats used by them, in a proportion of fifteeen out of seventeen, were

without difficulty inoculated with fatal anthrax, while their serum preserved mice inoculated with a mixture of blood and anthrax spores. Only the old rats showed a certain resistance to the bacteria, but their blood did not show prophylactic properties much more marked than those of younger animals, which were in general extremely susceptible. These experiments demonstrated that there was no relation between the preservative property of the blood of rats and their supposed immunity against anthrax. Similar conclusions followed the researches made upon other animals. Ogata and Iasuhara found their bacterial diastases in the blood of dogs and frogs, but the experiments of Enderlen and Peterman on the serum of the dog and those of Roudenko on the blood of the frog entirely upset the conclusions of the Japanese workers. In no case did the serum experimented upon appear to have any preservative properties.

Taking up the question from the point of view of the curability of anthrax by the serum of refractory animals, Erriquez and Serafini studied the action upon susceptible animals of the serum of the dog, of the rabbit, of the frog, and of the turtle. They did not make their mixture of the virus and of the blood beforehand, and their results were absolutely negative; they concluded, therefore, that in no case and in no way does the serum of animals naturally immune to anthrax exert the least protective action in susceptible animals. Under any circumstances, it appears necessary to conclude that anthrax infection is not from the point of view of orrhotherapy as conclusive a disease to study as it has been in a number of other bacteriological questions.

Hog Cholera.

The establishment of the preventive properties of the serum of animals vaccinated against rouget by Emmerich and Mastbaum, and the study by Chenot and Picq of the curative power of the serum of bovines in glanders of the guinea-pig, bring us to the results of Metchnikoff regarding the immunity of rabbits vaccinated against hog cholera. This disease, due to a bacterium studied by Salmon and Smith, Cornil and Chantemesse, and many others, is well understood to-day, and inoculated in rabbits, even in very small quantities, the microbe produces a rapidly fatal septicæmia. The injection of toxins secreted by this bacterium, as was demonstrated by Selander, gives the same picture as follows the injection of the bacterium itself, and the disease it produces in the rabbit is therefore at the same time an infection and an intoxication. In spite of the extreme susceptibility of rabbits, they can be easily immunized against the bacterium of hog cholera. It is sufficient to make a subcutaneous injection of a

very small quantity of the blood, that has been heated to 80° C., of an animal dead of this infection. Small doses repeated several times have been shown to confer a perfect immunity against a strong virus. Metchnikoff determined that the serum of animals thus immunized, injected either at the same point or at points removed from the site of inoculation, manifested constant preventive properties, and he attempted to solve the question as to what this remarkable power of the serum is due. The bactericidal action cannot be considered the cause, because the bacillus of hog cholera grows as easily, in the test tube, in the blood of immunized as in the blood of non-immunized animals; on the other hand, it is possible to find still living bacteria in the body of an immunized animal, many hours and sometimes many days after the inoculation, which proves that the fluids certainly do not possess a very active bactericidal action in the living animal; also, so far as the antitoxic properties of the blood are concerned, it may be demonstrated that they exist neither in the interior of the organism nor outside of it, for, in fact, virulent blood, which has been heated and left several hours in contact with the serum of the immunized rabbit, shows itself to be just as toxic as the same virulent blood simply diluted with water; on the other hand, the immunized animals were shown to be less sensitive than the controls to the action of the toxin of hog cholera, an evident proof that the latter is neither neutralized nor destroyed by the common properties of the blood. It is extremely difficult to make good experimental conditions for the study of the possible attenuating power of the serum of immunized animals, for in inoculating the virus cultivated on this medium, of necessity there is injected a small quantity of the medium itself, which might by manifesting its preventive properties make one believe in an attenuation of the bacterium, and, on the other hand, a faithful washing of the bacteria will surely bring on a considerable diminution in their number, which brings in the quantitative factor in the control experiments, the importance of which cannot be overlooked. But, inasmuch as death follows in all the experiments, although sometimes after considerable delay, it seems allowable to conclude that the serum of animals vaccinated against hog cholera does not possess any attenuating properties. This may be determined also indirectly; Selander has shown by his experiments that the virulence of the bacillus and the quantity of the toxin that it secretes in a given time are directly proportional; and Metchnikoff, sowing at the same time ordinary serum and serum coming from a vaccinated rabbit, has shown that after five days the two culture mediums heated to 60° possess toxic properties at least equal. These experiments lose a little of their importance, however, now that the attenuating power of the fluids is almost com-

pletely abandoned as a general theory of immunity. Whether this preventive power is a constant manifestation of the refractory condition of the immunized animal is an extremely important question from the point of view of the determination of the criterion of immunity. Metchnikoff's experiments seem to argue against this assumption. Rabbits treated by the serum presented a passing immunity, without their blood preventing in the least the progress of the disease in other animals, and, on the other hand, Metchnikoff has seen rabbits die of hog cholera whose blood was preventive in the dose of half a cubic centimetre. If the blood is neither bactericidal, nor attenuating, nor antitoxic, it must be admitted that it is not upon the bacterium itself that its action is exerted, but upon the organism of the inoculated animal. Metchnikoff showed in his experiments that for quite a long time it was possible to recover living bacteria englobed in the interior of the phagocytes, and he also showed that the number of leucocytes was above the normal in the blood of animals treated with serum, while it rapidly diminished in the controls, so that he felt himself justified in formulating the hypothesis that the preventive serum in the hog cholera of rabbits acted by stimulating the phagocytes, making them less sensible to the toxins and exciting them in their struggle against the bacteria.

Avian Septicæmia.

This work of Metchnikoff served as a model to other authors, for the clearness with which these important questions were put and settled made of this memoir on the immunity of rabbits against hog cholera a sort of general guide for the study of these curious properties of the blood serum. Sanarelli made use of this plan in his researches upon the genesis of the immunity of guinea-pigs vaccinated against the vibrio of avian septicæmia, which disease is easily transmissible to the guinea-pig, in which animal it takes on the appearance of an extremely acute septicæmia. Pfeiffer, Metchnikoff, Behring, and Nissen demonstrated the bactericidal power of the serum of immunized guinea-pigs as opposed to the inaction of control animals. This immunization is easily obtained by the repeated injection of culture bouillons sterilized at 120° C. This serum has both preventive and therapeutic properties. A dose of half a cubic centimetre at the point of inoculation, or of 5 c.c. when the injection is at a distance, is sufficient to protect the animals against the fatal disease, without producing anything more than an œdema or a slightly extended infiltration. Following out for a long time the experiments of Behring and Nissen, Sanarelli showed that, although most of the

vibrios seemed to disappear in the serum of vaccinated guinea-pigs during the first twenty hours, some that remained commenced to increase after the lapse of this time, and at the end of three or four days cultures on this medium were no less abundant than those in the serum of fresh guinea-pigs; thus, in the test tube, the bactericidal power is only relatively important, and it becomes absolutely *nil* in the living animal; in fact, before Sanarelli, Metchnikoff himself had demonstrated that in spite of this bactericidal power the avian vibrio, better known as the vibrio of Metchnikoff, developed in the organism of the immunized guinea-pig, and even acquired there the property of developing in the serum in the test tube, without being influenced by its hurtful action. The attenuating power cannot be regarded as the cause of the preventive power, for, far from diminishing the virulence of the bacterium, culture in the serum of immunized animals appears to increase the virulence in such fashion that the transfer of this culture on bouillon produces vibrios of a virulence almost always greater than the original. It also appears to be established now (as is pointed out by Achalme in his book upon immunity) that the stay of the bacterium in the body of a refractory animal almost always results in increasing its pathogenic properties; it would appear to be the same as regards the secretion of poisons, for the cultures upon the serum of an immunized animal always appear more toxic than cultures on normal serum, and, conversely, immunized animals, in spite of their preventive power, are more sensitive to the toxins of the avian vibrio, and are killed by doses too small to produce death in fresh guinea-pigs.

The researches of Sanarelli tend to support the hypothesis of Metchnikoff so far as the preponderating rôle of phagocytosis is concerned in the process of cure due to the action of the serum. He had already emphasized its importance in the genesis of the immunity of guinea-pigs. Sanarelli showed that in animals treated by the serum a leucocytosis appeared, more or less marked, but constant. The white globules, which did not appear except in very small quantity at the point of inoculation in the control animals, appeared in great numbers in guinea-pigs treated with the serum, and rapidly englobed the vibrios, which disappeared by intracellular digestion; in fact, the different phases of the process were absolutely similar to what occurs in hog cholera, and this almost absolute similarity of the experimental results in two perfectly distinct processes might lead one to regard the conclusions as of more general applicability than they actually are.

Symptomatic Anthrax.

These conclusions cannot be applied in all their details to all experimental diseases. It will be seen farther on that in diphtheria and tetanus, diseases of a wholly special character, the action of the serum is manifest in as striking a way upon the toxin as upon the bacterium itself, but there is another affection that cannot like these be considered purely toxic, one in which the mixture with the serum makes the most active fluid of the cultures entirely inoffensive; this is symptomatic anthrax (studied from this point of view by Deunschmann), due to the bacterium Chauvœi, a strictly anaërobic microbe. This affection, especially common among the larger ruminants, can be easily produced in the guinea-pig, to which it brings death in a few hours; rabbits, on the other hand, show themselves quite refractory to this infection. In order to reinforce their natural immunity, Deunschmann injected into the ear vein a small quantity of living virus, and when the animal had regained its weight there could be injected the same quantity of anthrax blood in the muscles of the chest; this produced a small abscess, after which the animal was refractory to the fresh inoculations. It is curious that the blood of new rabbits, in spite of their relative immunity, exercises no preventive action upon animals that are susceptible like the guinea-pig, and that the toxin secreted by the bacterium Chauvœi, of a sufficient activity to produce fatal results in the guinea-pig in the dose of 1½ to 2 c.c., shows itself equally toxic for the rabbit, an animal very resistant to the action of the living virus; the serum of immunized rabbits possesses, on the other hand, a very marked preventive power in protecting the guinea-pig in a dose of from 2 to 5 c.c. It is necessary, nevertheless, to wait some time after the inoculation of the animal before using its serum, for it would seem that the serum at first has toxic properties, and produces death in the guinea-pig in a dose of from 5 to 10 c.c. The preservative action, much less marked than in hog cholera and in avian septicæmia, may, nevertheless, show itself if the serum be injected at a distance, or a little while before the inoculation of the virus; in no case is it able to arrest or modify the progress of the disease once started. The interest of Deunschmann's work is especially in the action of the serum upon the toxin of symptomatic anthrax. This toxin produces a very intense necrosis, which is entirely neutralized when an equal volume of the preventive serum is mixed with the fatal dose. In certain cases, also, the serum was found efficacious when injected an hour before the toxin. It is a long way from this anti-

toxic action to the prodigious power of the antidiphtheritic and the antitetanus serum, but, nevertheless, the researches of Deunschmann show in symptomatic anthrax an interesting transition between the diseases in which the antitoxic power is absolutely nothing, and those in which it seems at first sight to exercise a preponderating action. If these somewhat inconclusive researches appear to have been unduly noticed, it is only to demonstrate how much too quick generalization there has been in bacteriology, and that, although the laws remain the same, it is foolish to reason in regard to one bacterial affection upon the basis of experiments made upon a different disease. It is certainly to these too hasty conclusions that are due the many false theories that have obscured the history of immunity, which is at the same time so simple and so complex (Achalme).

Serum Treatment in Human Disease.

Tuberculosis.

Richet and Hericourt after their discovery of the curative properties of the blood of the dog against the infection of the staphylococcus pyocyaneus attempted to apply this phenomenon to human therapeutics, using tuberculosis for their test. They showed, in 1888, that by transfusing the blood of the dog into rabbits, the progress of tuberculosis was retarded in the latter, and that it could even be arrested if the transfused blood came from dogs previously subjected to a bacillary infection, an infection from which they readily recovered. The application of this procedure was made in man, and in 1891 Richet and Hericourt reported an encouraging but inconclusive series of results. Many other authors who tried the new method showed that while there certainly was a slight temporary amelioration the disease soon began again its usual progress. Partial, irregular results were obtained by Bertin and Picq in studying the antituberculous qualities of the blood of the goat. The amelioration obtained was not specific, and the injection of the serum of the dog appeared to have stimulating properties that were at least as favorable in other diseases as in tuberculosis. One error, it was suggested, was that at this time there was no difference made between the bacillus of human tuberculosis and that of avian tuberculosis; because the latter was much more easily cultivated on artificial media, it was almost exclusively employed in laboratories, and it was with this bacillus that Richet and Hericourt experimented. More recently there have been made out certain distinctive characteristics that would lead one to suppose that the two affections are not identical, and that, therefore,

it is impossible to generalize as to the experimental results obtained from one in regard to the other; and further, the experiments of Colin and Nocard and others have demonstrated that the goat cannot be considered as an animal that is refractory to tuberculosis, and therefore it is not to be wondered at that the results were irregular. Unfortunately, it was impossible to find among the experimental animals those that are actually immune to human tuberculosis, and, therefore, it was attempted to secure artificial immunity, but the difficulties that have been found in the way have been very great. Courmant, and Richet and Hericourt have reached a result that is very interesting, namely, that dogs inoculated with the bacillus of avian tuberculosis, while showing but very slight reaction, acquired a considerable resistance to human tuberculosis. It is possible that something may be made out of this discovery, but, unless the results of Maragliano with the serum of the horse prove to be all that has been claimed for them, we must admit that as yet but little advance has been made in the direction of the effective handling of tuberculosis by means of serum.

Rabies.

The serum method of treating rabies is very distinct from that of Pasteur of handling the same disease. Most of the work in this direction has been carried on by Babes and Lepp, without any very satisfactory issue. Their results, however, had a very great theoretical interest so far as the general applicability of the idea of serum therapeutics is concerned, since they demonstrated its efficacy in a disease so widely separated as is rabies from the ordinary infectious diseases. The more recent researches, but still as far back as 1892, seem to demonstrate the efficacy of the serum of animals inoculated against rabies, but they are especially interesting as demonstrating the fact that the serum of such animals is particularly efficacious in animals of the same species.

Typhoid Fever.

In spite of the fact that the absolute proof that the bacillus of typhoid fever is the cause of the disease has not been furnished, the collateral evidence is so overwhelming that there can be no longer any doubt. Brieger, Kitasato, and Wassermann were the first to demonstrate the preventive or curative properties of the serum of animals vaccinated against typhoid fever. Many others have also studied the question. The work of Sanarelli and Chantemesse and Widal is that which has specially determined the remarkable properties of the blood of animals vaccinated in typhoid fever. From their

results it has been shown that whether one injects at the same time, or a little before the inoculation of the virus, a very small quantity of serum taken from an immunized animal, the development of typhoid fever is made almost absolutely impossible. One-half a cubic centimetre is sufficient when the inoculations of the virus and of the serum are made at the same time, while nearly 2 c.c. is necessary, if the injection be made at a different point or before the introduction of the bacillus. The rapidity with which experimental typhoid fever develops in the guinea-pig made it probable that the serum would be unable to arrest its progress, but, nevertheless, inoculation within an hour after the infection almost certainly arrested the disease. Experimenting as did Stern upon the properties of the blood of human beings who had acquired immunity to typhoid fever by previous attacks, Chantemesse and Widal reached the same results; six times out of six the serum manifested an active curative power, and this power was the stronger the nearer one was to the attack. Five times out of seven in the experiments of Stern the serum was active, coming from persons whose typhoid fever had occurred from two days to a year previous; three times out of seven when the attack had been from one to seventeen years previous; and, finally, twice out of fourteen times the serum of persons who had never been attacked with typhoid fever showed a marked antityphic power. Chantemesse and Widal found this once out of three times. These laboratory experiments were so conclusive and encouraging that attempts have been made to apply them to typhoid fever in human beings, but without very great practical results. Bruschettini attempted to demonstrate that the blood of rabbits inoculated against the typhoid bacillus presented in the test tube in contact with this bacillus bactericidal properties much more marked than those of the serum of normal rabbits; but Stern, experimenting upon human blood, reached results diametrically opposite, and demonstrated that the typhoid bacillus grew with greater facility in the serum coming from persons who had had typhoid fever than in those that had not. These latter experiments have been shown to be, for the same reason, incorrect, and the observations of Bruschettini and others have been made use of quite recently by Widal and others in the elaboration of the method of serum diagnosis of typhoid fever.

Pneumonia.

The Pneumonic Toxin.—The disease produced by the pneumococcus is an infection more properly than an intoxication, analogous to that of tetanus or of diphtheria, and, in fact, the pneumococcus does not appear to secrete either very abundant or very active toxins.

Cultures very slightly toxic during the first three or four days become most active later, especially when the acid reaction is apparent. Foà and Bonome, and G. and F. Klemperer succeeded in isolating immunizing substances rather than toxic. Issaeff, recognizing that the toxicity of the cultures was proportional to the virulence of the bacteria, attempted to increase the latter by successive transmissions through the peritoneum of rabbits. At the end of ten or twelve inoculations, the blood of the last of the series loses its power of coagulation, and becomes extremely toxic and purulent. Issaeff secured this blood under aseptic conditions, treated it with an equal bulk of sterilized water which was slightly alkaline and contained one per cent. of glycerin, and then passed it through a Chamberland filter; this product was sufficiently toxic to produce death in rabbits in a dose of one one-hundredth of the weight of the animal.

Antipneumonic Serum.—Foà and Carbone, then Emmerich and Fawetzky showed that it was possible to immunize and even cure rabbits or mice inoculated with the pneumococcus by means of the serum of immunized animals, and every other experimenter who has since tried the same thing, the Klemperers, Krouse and Panzini, Issaeff, and many others, reached the same result. The serum possesses a very great activity, two to four drops of the serum of a vaccinated rabbit taken on the twenty-fourth day of the immunization being sufficient to protect a mouse against the fatal disease, and a dose of 8 c.c. of the serum of immunized rabbits being sufficient to arrest the pneumococcus septicæmia in twelve rabbits twenty-four hours after infection, in the hands of the Klemperers. There is, of course, some ground for questioning these results, because it is possible that the Klemperers did not use a sufficiently strong culture; but no matter what objections may be raised, the therapeutic property of the blood of immunized animals is beyond question. Its interpretation has varied according to the experimenter, and the general theory of immunity that he adopted; Foà and Carbone, and Emmerich and Fawetzky believed it to be due to bactericidal action; but this bactericidal property could not be demonstrated by the researches of Behring and Nissen, or by those of G. and F. Klemperer, while the serum of the normal rabbit inoculated with the pneumococcus becomes rapidly cloudy and turns acid, forming a heavy layer at the end of forty-eight hours at the bottom of the tube. The serum of immunized animals preserves for a long time its clearness and alkalinity, and it is only after several days that the culture makes its appearance, progressively turning the medium acid, and preserving for six or seven weeks its vitality and its virulence, which properties disappear at the end of three or four days in the serum of control

animals. The morphology of the bacteria is not very greatly modified, and it is, therefore, determined that there is a difference between the blood of fresh animals and that of immunized animals considered as culture media. Is it necessary, nevertheless, to attempt to attribute the action of the therapeutic serum to this so-called bactericidal property, which only imperfectly opposes the growth of the bacteria? If this were so, it would be necessary that all media, and they are very numerous, that do not furnish an excellent soil for the development of the pneumococcus should also be endowed with preventive properties; but the serum of the dog, which is an animal moderately susceptible to the pneumococcus, exercises an action upon the development of this bacterium analogous to that of the serum of vaccinated rabbits, and Foà and Scabia showed that the serum of the dog previously inoculated with the pneumococcus does not exert on the rabbit or the mouse any preventive action.

Furthermore, the more striking results obtained with the vibrio of septicæmia showed that, so far as the bactericidal power is concerned, it was not possible to generalize from facts observed in the test tube as to what goes on in the organism itself; Issaeff, indeed, found that it was possible to recover living bacteria in the œdema of rabbits inoculated eighteen to twenty-four hours before with the virulent pneumococcus, although the cultures so obtained were not virulent. The bactericidal property not furnishing a sufficient explanation, it was suggested that the serum of vaccinated animals acted not on the vitality, but on the virulence of the bacterium, and that its preventive power should be ascribed to its attenuating properties. Roger carried out experiments bearing upon this point, and Issaeff showed that after washing the bacteria to remove the serum that adhered to them (the existence of the capsules making the separation difficult), in spite of a considerable diminution in the number of the bacteria, death was produced in animals thus inoculated in a much shorter time than in those that had received an unwashed culture. In other experiments he showed, on the other hand, that the pneumococcus secreted its toxins as well in the serum of vaccinated animals as in the other media, and that bouillon cultures of pneumococci developed on primitive serum always were more virulent than the mother culture; so that it appears that the serum of vaccinated animals does not exert any attenuating action upon the bacterium of pneumonia. The hypothesis of an antitoxic action remains, and it is this that the Klemperers took up in their remarkable work, reaching this conclusion, as the result of experiments in the test tube upon the neutralization of the toxins of the pneumococcus by the serum of vaccinated rabbits; but the feeble virulence of the culture

with which they made their experiments make their results more or less uncertain, for Issaeff, working with toxins much more active than those of the Klemperers, showed that the mixture of the pneumococcic virus with the serum of vaccinated rabbits was just as toxic as when it was diluted with an inert medium. On the other hand, it is not possible to admit that the serum of vaccinated animals can act upon the toxins in the organism, for these animals have always appeared more sensitive to the pneumococcic toxins than the controls. According to this line of argument, therefore, the antipneumonic serum is neither bactericidal, attenuating, nor antitoxic. To these negative conclusions, Issaeff affirms the stimulating power that the serum of immunized animals exercises upon phagocytosis, for in animals treated by the serum there occurs at the point of inoculation a very marked but very fleeting œdema, which disappears completely in twenty-four hours, and which may be shown to contain a number of phagocytes; in control animals, on the contrary, the local œdema lasts much longer, the diapedesis of the leucocytes is much more marked, and the phenomena of phagocytosis are difficult to demonstrate. The application of these results to pneumonia in man was first made by G. and F. Klemperer by injecting in the pneumonic patients the serum of vaccinated animals, and their results appeared to be very encouraging. Shortly afterwards Foà and Carbone, and then Foà and Scabia, studied a series of cases which appeared to give encouraging results; and others following them have obtained such success that the encouragement for further research is very great, and it is probable that, if such great difficulty in securing the serum of immunized rabbits did not exist, the observations already made would have been much more numerous. They are not likely to increase very rapidly, however, until a more abundant source of active serum can be found.

Antistreptococcic Serum.

In spite of the enormous importance that the streptococcus has in human pathology, comparatively few attempts have been made to obtain a serum active against this microörganism. The difficulties surrounding the investigation are very great. If one believes that it is in accordance with its virulence, and the point of inoculation, that the streptococcus produces septicæmias, erysipelas, suppurative inflammations, etc., if, in other words, one believes that all streptococci are the same, the question even then is not a simple one; if, on the other hand, one believes that the varying clinical manifestations produced by the streptococci are due to varying species of bacteria, the simplicity of the question disappears entirely. Vaccination

against the streptococcus is extremely difficult. Lingelsheim and Behring failed in their attempt, Roger only partially succeeded, Mirornoff obtained extremely inconstant results. Apparently the first effective immunization of animals with any streptococci was secured by Marmorek, from whose experiments it is possible to draw the first encouraging conclusions in this direction, but, at the best, the results obtained have not been so successful as it is to be hoped they will soon be.

Cholera.

The work upon cholera began, or could begin, only with the discovery by Koch, in 1884, of the specific bacterium of the disease. While an enormous amount of disputation in regard to this microorganism has been carried on, the general opinion to-day is that it is the cause of the disease, and any results as regards immunity would, therefore, be dependent upon a study of this spirillum. So far as European observers are concerned, these results have not apparently been very satisfactory.

In the first place, as regards the toxin of cholera, the spirillum always secretes, whenever it secures a foothold in the intestine, a toxin which, upon being reabsorbed, destroys by intoxication of the organism. Westbrook made an especially elaborate research in order to determine the chemical nature of the toxin, after having established, as had others before him, that upon albuminous materials the cholera spirillum secretes a substance that in guinea-pigs, according to the dose, may kill or immunize them. He grew the spirillum upon a medium containing no albuminoid substances, in which the azote nutriment was represented by asparaginate of sodium; after filtration the fluid showed the same immunizing and toxic properties, although the presence of proteid material could not be shown by the biuret reaction. This tended to demonstrate that, according to the opinion long before expressed by Duclaux, the albumoses, toxalbumins, and so on, regarded by various authors as pure toxins, are nothing less than mixtures of toxins and proteid materials; the nature of the former remaining still unknown, but apparently allied to the diastases.

Anticholeraic Immunization.—There is no doubt that the anticholeraic serum possesses, even in very small doses, the property of preventing the disease in guinea-pigs, and this vaccination is relatively easy to obtain. The researches of Ferrán, Gamaleïa and Haffkine have shown that the inoculation of attenuated virus was able to fortify the animals against a later infection. Haffkine has endeavored to apply anticholera vaccination to human beings, making use of cultures attenuated by continued aëration, and injected into the subcuta-

neous tissue. The bacteria in the inoculated fluid are killed by the action of carbolic acid, and it has been found that the same results may be obtained by the injection of small quantities of filtered cultures. At first sight it would appear as if vaccination against cholera in the human being ought to be easy, but there are two difficulties. In the first place, the spirillum is probably only one species, and in cholera of various origins there are differences of form, motility, and virulence that appear to force us to admit the existence of distinct races of bacteria; therefore, it is a question whether an animal immunized against one of these races is immunized against the whole series, though it is probably so in most cases, for Gamaleïa has seen that animals vaccinated against the avian vibrio (vibrio Metchnikovii) are also vaccinated against the spirillum of cholera, and similar results have been obtained by others. The chief difficulty, however, is the difference which exists between the experimental choleraic peritonitis of the guinea-pig and human cholera. In the first of these affections, the bacterium is found in the tissues, where it develops freely if nothing occurs to prevent, and it produces a typical infection in these animals; but in man the condition of things is very different: the bacterium remains, so to speak, outside of the organism. It develops in the intestines, where, even if it occurs at all, phagocytosis cannot be very active, and there secretes its poisons, which upon absorption give rise to the phenomena of choleraic intoxication. The two conditions, therefore, are entirely different, and the question would arise whether the preventive measures that are efficacious against one would be active against the other; however this may be, the enthusiastic reports of the results of Haffkine's inoculations against cholera in India would lead us to suppose that the practical application of experimental results had been more successful than the experimental results themselves might warrant us in hoping for.

Tetanus.

Tetanus and diphtheria are the two diseases to which most attention has been paid, so far as immunizing human beings is concerned. Many authors, including Nicolaier, Flügge, Rosenbach, Nocard, Brieger, and others, have worked upon the tetanus toxin, which was especially studied by Vaillard and Vincent, in 1891. It is easily to be obtained by filtering through porcelain bouillon in which has grown the bacillus of tetanus, and extremely strong fluids can be obtained by making a number of generations of bacteria grow in the same bouillon. Figures are almost powerless to give an idea of the enormous strength of this toxin; a thousandth of a cubic centimetre

will kill an adult guinea-pig, and a hundred-thousandth will rapidly prove fatal to a mouse. When one understands that out of 1 c.c. of the bouillon there can be obtained upon evaporation scarcely 0.025 gm. of organic matter, that is necessarily not all toxin, it can be seen that the dose of the tetanus toxin necessary to kill a guinea-pig is less than 0.000025 gm., and that for a mouse one reaches the inconceivable amount of 0.00000025 gm. Man himself would appear to be one of the most sensitive animals to the tetanus bacillus. Thus we have the account of a French observer who scratched himself very slightly with a syringe needle barely moistened with the filtered fluid of the tetanus culture, and in spite of the almost infinitesimal amount inoculated was affected with a typical generalized tetanus at the end of four days. Various opinions as to the nature of this poison have been expressed. It has been considered a ptomaïn, then a toxalbumin, and finally a diastase; the latter opinion being based upon its extreme activity, its sensitiveness to heat, and the ease with which it fixes itself upon amorphous precipitates. Courmont and Doyon carried the analysis further, basing their observation upon the fact that tetanus poison needs, no matter what the dose, a certain period of incubation. They think that the tetanus toxin is not toxic of itself, but that this property resides in the secondary products that it produces by fermentation in the tissues. This fermentation, which requires certain conditions of temperature, as was shown by experiments upon frogs, produces a substance resembling strychnine, not destroyed by ebullition, which they found in the muscles, the blood, and the urine, and which would produce death without the need of any period of incubation. If these conclusions should be verified, they will certainly throw new light upon many obscure points in tetanus as well as in other toxic diseases.

Immunization.—The doses in which the soluble products of the tetanus bacillus are toxic for animals are so small that another method of obtaining immunity is to be followed than the ordinary one consisting in the use of sterilized cultures. Behring and Kitasato succeeded in producing immunity to tetanus by following the inoculation with an injection of a solution of trichloride of iodine; later they added the trichloride to the tetanus toxin, and after a definite period of time injected the mixture, but the results were uncertain, many animals dying under the inoculations. Brieger, Kitasato, and Wassermann inoculated a mixture of a culture of tetanus spores and bouillon from the thymus gland, of the first one part, and of the second two. Vaillard and Roux later adopted a method of adding the toxin to water containing one five-hundredth part of metallic iodine, and mixing it with the filtered culture fluid in a proportion of one to

five; 4 c.c. of this mixture could be injected into a rabbit without accident, and upon injecting every three days a mixture in which the iodine water was in a continually diminishing proportion, it was possible to increase gradually the dose of the tetanus toxin, and to obtain with certainty complete immunity. Guinea-pigs and rabbits had to be immunized with very much smaller doses to begin with. The most curious phenomenon resulting from these different methods of immunizing is beyond question the antitoxic power of the serum of the vaccinated animals. It is not possible to believe that this antitoxic power is entirely a function of the refractory condition of the animals; for example, Vaillard demonstrated that in vaccinating a rabbit, not with the toxin, but with gradually increasing doses of tetanus spores well washed, and with a little lactic acid added, it was possible to immunize this animal completely, while its serum did not become antitoxic, and he also demonstrated that the blood of chickens naturally refractory to the bacterium of tetanus possesses no antitoxic power, but that it acquired this power as a result of the injection of the tetanus toxin. Behring and Kitasato were the first who demonstrated the antitoxic property of the blood of animals vaccinated against tetanus. In their first note in 1890, they advance the following propositions: 1. The blood of a rabbit refractory to tetanus is capable of destroying the tetanus toxin. 2. This property can be demonstrated in the blood drawn from the vessels and in the serum, freed of all cells, which comes from it. 3. This property is so lasting that it persists even after transfusion into other animals, and it thus permits of the use of the serum in the treatment of the disease. 4. This property is not present in the blood of non-refractory animals, and the tetanus bacillus can be found after their death in the blood and other fluids. Unfortunately, control experiments made it necessary to be a little more guarded in these statements. Tizzoni and Cattani, in 1891, made some limitations so far as the cure of animals already in the stage of contracture; and Kitasato, in 1892, acknowledged that, while the antitoxin was extremely efficacious when injected before or a little while after the toxin, it was often inefficacious when employed towards the end, or after the appearance of the tetanic symptoms. The results of more recent work by Behring and others have shown that the cures of tetanus with serum are not so frequently obtained nor so prompt as it had been hoped they would be. Roux and Vaillard reached the following conclusions: 1. The antitoxic serum will surely prevent tetanus even in very small doses when it is injected before the tetanus toxin. 2. When the serum is injected at the same time as the toxin, a local tetanus is usually seen, even when the quantity of the serum

injected is very great. 3. When the serum is injected after the toxin, but before the appearance of any tetanus symptoms, there is always a local tetanus, and the dose of serum necessary to prevent death is much greater than when it is injected soon after the infection; after a certain time has elapsed, varying with the animals, prevention is not possible even with large quantities of serum. 4. Tetanus is more or less rapid in its onset, and therefore more or less difficult to prevent, according to the place where the injection of the toxin is made; inoculations in the thorax or abdomen are more rapidly fatal than those made in the extremities. 5. When the infection is produced by the tetanus bacillus developing in the tissues, the prevention depends upon the quantity of serum injected, and the time which has elapsed from the moment of injection of the virus to that of inoculation of the serum; it fails most often when the animals are inoculated in a manner to have a rapid tetanus, but it succeeds in the mild infections; in these cases prevention is not always absolute, and if the focus is not removed the disease which appears to be arrested may take up its course, and death may then occur after a very long time. Unfortunately, and contrary to the first opinion of Behring and Kitasato, the results obtained in attempting to cure declared tetanus in animals are not so encouraging as those following attempts at its prevention. Vaillard and Roux have, in fact, shown that it is extremely difficult to cure declared tetanus in animals, and they say in explanation that, at the moment of the appearance of the first symptoms, the quantity of toxin elaborated is most frequently sufficient to destroy the animal in its action upon the cells, and the antitoxin can do nothing against a poisoning already completed. Large doses of a very active serum have always proved powerless against a tetanus taking a rapid course, but notwithstanding this, experiments in the curative use of the serum in human beings have been sufficiently encouraging to warrant its employment in any case when it can be obtained. The experiments of Courmont and Doyon upon the nature and mode of action of the tetanus poison lead them to believe that it is not to the toxin itself that the accidents of the disease are due, the toxin acting only as an *enzyme*, producing a fermentation in the tissues, but it is the products of this fermentation endowed with toxic properties that act directly upon the nervous elements. Reasoning from experiments made upon the frog under different conditions of temperature, they conclude that warmth is necessary for the production of this fermentation, the frog not becoming tetanic if it be kept at a low temperature after the inoculation of the toxin. They rely for the support of their conclusions upon the presence of a substance, acting like strychnine, in the bodies of animals dead of

tetanus, and upon the constant existence of a latent period between the injection of the toxin and the appearance of results, no matter what the dose of the poison employed. If these opinions be adopted, it is easy to understand the inefficacy of treatment after the symptoms have appeared, since the action of the serum is especially upon the enzyme, preventing or modifying the fermentation, the source of the toxic products, either directly or by putting in action the means of defence of the organism; but once the strychnine-like poison has formed, the serum is useless against it.

Diphtheria.

The Diphtheritic Toxin.—In animals dead of diphtheria, the bacilli are not found in numbers, except at the point of inoculation, and in no case do they invade the whole organism as do the bacilli of anthrax. The question therefore arose, how it was possible for the disease to produce the death of animals in so short a time as it did. Loeffler and Oertel suggested the hypothesis of a poison secreted by the bacteria, and Roux and Yersin furnished the experimental proof of the existence of a diphtheritic toxin by filtering cultures, and reproducing the picture of the disease by the injection of the fluid thus freed of bacteria. It is frequently possible in this way to kill guinea-pigs, rabbits, and even dogs in twenty-four hours; upon examination there is found at the point of inoculation an œdematous exudate, the lymphatic glands are congested, the small intestine, lungs, and suprarenal capsules are hyperæmic, and the pleural cavity often contains a serous fluid; if death is less rapid, the most marked symptoms are progressive cachexia and diarrhœa, and the liver usually becomes fatty degenerated; with still smaller doses, it is possible to produce paralyses precisely like those that are to be observed in man, which may terminate fatally or may go on to cure. The culture media may present very considerable variations in toxicity. In their first memoir, Roux and Yersin speak of the injection of 30 c.c., while later Roux and Martin considered the dose of one-tenth of a cubic centimetre should be the standard, and should produce death in forty-eight hours in a 500-gm. guinea-pig; and still more recently, toxins of very much greater strength have been obtained, so that even one one-hundredth of a cubic centimetre, or less, has been fatal to guinea-pigs of this size. The causes of this variation in the strength of the toxins produced have been the subject of much study. The first, and perhaps the most important cause, is the age of the culture; at first, when the bouillon becomes acid, no trace of the toxin is found; later, when the alkalinity appears, probably due to the oxidation of the

organic material, the toxin develops rapidly. Free access of air is an important factor in the production of toxin, and certain experimenters lay great stress upon the necessity of the absence of muscle sugar in the meat from which the bouillon is prepared. It is interesting to recognize that most of these conditions are those which the bacilli of diphtheria encounter in the false membranes in the respiratory tract, and in this way may be explained the rapid intoxication which they produce. The production of the toxin was supposed also to be proportional to the degree of virulence of the bacillus, but less importance is placed upon this point now than in the early experiments upon this subject. The fluid after being filtered through a Chamberland filter may preserve its toxicity for a very long time, if kept in closely stoppered bottles and away from the light. The influence of air and of light has a marked effect upon the toxin. Roux and Yersin showed that a fluid toxic for guinea-pigs in a dose of one-eighth of a cubic centimetre killed them only very slowly, and in a dose of not less than 1 c.c., after two hours' exposure to the sun in vessels opened to the air, and produced only a local œdema after five hours; while the same fluid exposed to the sun for the same length of time, in well-closed tubes, lost only a small part of its toxic power. Heat also acts very powerfully upon the diphtheritic toxin; an exposure to 120° C. for twenty minutes makes it harmless, or at least weakens the poison so that it kills animals only very slowly and in very large doses. The acidity of the medium is a very unfavorable condition for the action of the diphtheria toxin. It has been seen that while acid the cultures were only slightly toxic, and it is possible to diminish their action very considerably by adding to the fluid small quantities of lactic or tartaric acid, sufficient to render an injection of 1 c.c. active in a guinea-pig. The neutralization of this added acid brings back incompletely the previous toxic power of the cultures. Certain chemical agents also act upon the diphtheria poison; the peptic ferments, such as pepsin or trypsin destroy it, prolonged contact with alcohol modifies it very greatly; but the most powerful agents are the oxidizing ones, permanganate of potassium destroying the diphtheria toxin completely, while reducing agents have no influence on it; the alkaline hypochlorites and the chlorite of calcium modify it, but in a less regular manner than iodine, the latter acting as in the case of the tetanus toxin. The addition of Gram's mixture to the diphtheria toxin enables animals to withstand otherwise fatal doses, and it is upon this property that the method of immunization that is used at the Pasteur Institute is based. This toxin, so called, is merely the culture fluid filtered through porcelain. Further analysis has not yet determined its exact nature. Roux and Yersin suppose it to be a

diastase, while Brieger and Fraenkel considered it a toxalbuminoid that can be precipitated after treating the filtered fluid with alcohol. Inoculated in animals this was toxic in a dose of 10 mgm. They considered this to be the pure toxin, but their conclusions are apparently not well founded. The size of the dose necessary to secure a fatal result would seem to indicate that the poison obtained by Brieger and Fraenkel was certainly impure, for Roux and Yersin isolated a product which they considered impure, but which killed guinea-pigs in a dose of two-tenths of a milligram. Guinochet and Ouchinsky have directly weakened the hypothesis of the albuminoid nature of the diphtheria toxin by cultivating the bacillus of diphtheria on alkaline secretions, and obtaining cultures possessed of a certain toxic power which did not contain any proteid material, so that the evidence tends in the direction of Roux's hypothesis of the diastatic nature of the diphtheria poison.

Immunization.—Roux and Yersin failed in their attempts at vaccinating animals against the diphtheria bacillus or the diphtheria toxin. C. Fraenkel succeeded in immunizing guinea-pigs against the subcutaneous injection of virulent cultures, but not against diphtheria of the mucous membranes. To obtain this result, he heated the fluid containing the toxin for an hour to 65° or 70° C., and injected 10 to 20 c.c. under the skin or into the peritoneum of guinea-pigs; these grew somewhat thin, then at the end of fifteen days were sufficiently immunized to receive without trouble pretty considerable doses of virulent cultures. Fraenkel worked upon the idea at that time somewhat believed in, that this degree of heat destroyed the toxic material and allowed an immunizing substance to remain, which latter was destructible only by raising the temperature to from 90° to 100°, but nothing has occurred since that time to support that hypothesis. Shortly afterwards appeared the first work of Behring on antidiphtheria vaccination; in this he gave four new procedures for immunizing animals as follows: 1. The injection of virulent cultures, or filtered cultures with the trichloride of iodine added. 2. The injection of the pleuritic exudate of guinea-pigs that had died of the diphtheria infection. 3. The infection of animals by the diphtheria bacillus with later treatment by the trichloride of iodine. 4. The preliminary treatment of animals with oxygenated water. These various methods failed to give successful results in the hands of other experimenters, with the exception of that of the trichloride of iodine, and this method demands such precautions that almost a year is necessary to reach a very slight degree of immunity. So slight were the results from these methods, that as late as July, 1892, Behring, Kitasato, and Wassermann wrote that there was no certain method

known for immunizing against diphtheria. The lack of success in most of these experiments lay in the choice of animals which were the most susceptible to diphtheria, so that their immunization was as difficult as their susceptibility was great, and it was not until less susceptible animals, as the dog, were used, by Aronson and Bardach as well Behring, that great success was obtained.

In 1892 Behring and Wernicke suggested two new methods, the first that of inserting under the skin of rabbits the precipitated phosphate of calcium dried, powdered, and previously heated to 77°; the second, the ingestion of the diphtheria poison and its absorption by the digestive tube. Wernicke secured immunity, or thought he did, by feeding a dog upon the flesh of immunized sheep; the animal thus nourished appeared to be refractory, but the immunity was not very durable. He succeeded also in immunizing dogs by the injection of old cultures, at first with carbolic acid added, then pure, followed by increasing doses of a very virulent culture. Roux, meanwhile, carried on his investigations, which were communicated to the International Congress of Hygiene and Demography at Budapest. He selected the horse, which is comparatively easy to immunize, and which furnishes a large supply of serum. He employed the method used by Roux and Vaillard in tetanus immunization, consisting in adding to the toxin trichloride of iodine, which diminishes its toxicity to a very great degree. In the beginning there is added to the toxin one-tenth by bulk of Gram's solution, and a quarter of a cubic centimetre of this mixture is injected into the horse, and if no reaction is produced, the dose may be increased within a day or two to half a cubic centimetre, and so on, up to 1 c.c.; then the pure toxin may be used in a dose of a quarter of a cubic centimetre, gradually increasing until 5 c.c. has been reached; then the horse may be considered as refractory. The immunity is still further increased by inoculating increasing doses of the poison, and these are pushed so far that at the end of two or three months the animal is able to withstand without any reaction whatever at least 250 c.c. of the filtered culture.

Antidiphtheritic Serum.—The paper of Behring and Kitasato, published in December, 1890, marked the beginning of a new era in the history of serum therapeutics. In this paper, they made these four statements: 1. The blood of an animal immunized against diphtheria is able to destroy the poison of the disease. 2. This property can be demonstrated in the blood taken from the vessels and also in the serum which comes from it freed from all corpuscles. 3. This property is so durable that it persists even after transfusion into other animals, and can thus be used in the treatment of the affection. 4. This property is wanting in the blood of non-refractory animals, and

the poison can be discovered after their death in the blood and other fluids.

These propositions are, of course, the same as those that applied to tetanus, but they form the beginning of the first definite and successful attempts in the application of serum in therapeutics. Many observers, Behring and his assistants, including Wernicke, Boer, Kossel, and Knor, have carried out experiments proving the truth of these propositions. As in the case of tetanus, the mixture of the diphtheria toxin with the serum of immune animals can be injected into other animals without producing any unfavorable result. The previous injection of the serum also preserves them from the effects of many times the fatal dose of the toxin. In no case, however, has the serum of animals most perfectly immunized shown itself as active as that of horses immunized against tetanus; in fact, while in the latter it is possible to obtain a serum which is active in a dose of the one-hundred millionth, the preventive power of diphtheria serum does not surpass in most cases a one-hundred thousandth; but it is interesting to know that, even if the antitoxic and preventive properties are more feeble, the curative action is much greater, for, whereas in tetanus the use of the serum is for the most part useless after the symptoms have appeared, it is possible to save animals attacked with diphtheria, even when the disease is well advanced. Experimentally, the amount of serum necessary to preserve animals inoculated with toxin is proportional to the time that has elapsed since the introduction of the poison; after twelve hours the serum seems to be powerless, and the animals die very little later than the controls, but the serum appears to be much more active if cultures are employed rather than the toxin, a condition that to the French appears more nearly to approach the clinical conditions. It is possible to cure guinea-pigs by treating them twelve to eighteen hours after the infection, when the controls die in from twenty-four to thirty hours; so long as the temperature is elevated and has not shown the ante-mortem depression, the injection of large quantities of serum may be curative. In order to come as near as possible to the varying clinical conditions, Roux and Martin among others studied the effects of the serum upon diphtherias complicated by association with other bacteria; that with the streptococcus is especially frequent and severe, and inoculation in the trachea of a rabbit of a mixture of streptococcus and diphtheria bacillus produces death in twenty-four hours, the result of broncho-pulmonary inflammations. Under such conditions, the cure is much more difficult, and the use of the serum must be very prompt. In the experiments of Roux and Martin, only those animals were saved in which the serum was used at most six hours after the inoculation,

and at this extreme it is necessary to use a number of injections; after twelve hours any intervention appeared to be useless. The experimental results justified beyond question the use of the antidiphtheritic serum in human beings, and the results of this clinical use have even surpassed the hope that was aroused by the laboratory experiments.

Serum Treatment in Human Diphtheria.—The first attempts were, however, not very encouraging, and in 1892 Henoch reported the negative results that he had obtained with the antitoxic serum of Behring. The first statistics published were those of Schubert, 34 cases, with a mortality of 18 per cent., and those of Canon, 15 cases with 20 per cent. mortality; Cosel reported the use of the serum in 233 children, with 33 per cent. mortality, and he showed that the number of deaths was very much less the nearer to the beginning of the disease the treatment was made, having had 100 per cent. recoveries in patients above nine years of age. Korte published the results in 121 children treated in the Urban Hospital in Berlin, the mortality being 33 per cent., while it ran up to 53 per cent. in another series of 106 treated by the ordinary methods. These patients were treated with serum prepared by Behring. Soon after, Katz and Baginsky, using Aronson's serum, showed a mortality of 13 per cent. in a series of 128 cases of children under Katz, and in another of 163 cases under Baginsky. Roux published later the results obtained under his direction by Martin Chiallou in the Hospital of the Infant Jesus in Paris. The most careful bacteriological and clinical observations were made, and the conclusions were therefore very much more important than any that had been previously published. Of 300 cases forming the basis of the report, 169 were of anginas without any broncholaryngeal complications, and 131 were of actual diphtheritic croup. In the first set, the anginas due only to the diphtheria bacillus, and those with other bacteria associated, are to be differentiated; the first were 120, of whom 9 only died, and of these 9, 7 died during the first twenty-four hours in the hospital; if we throw them out, there results a percentage of mortality of 1.7, as against 41 per cent., which was the mortality before the introduction of the diphtheritic serum. In the total of the 300 cases of diphtheria, of all kinds, there were 78 deaths, about 26 per cent., while former statistics gave a mortality of 50 per cent. and over, which mortality rose to 60 per cent. at the Trousseau Hospital during the six months that the serum treatment was being experimented with at the Hospital of the Infant Jesus. These results have only been confirmed by those reported from all parts of the world since that time. Thus in the Boston City Hospital, where the mortality before the use of serum ran between 45 and

50 per cent., the mortality since the use of the serum has been between 13 and 14 per cent.

The Mode of Action of the Antidiphtheritic Serum.—After the discovery of Behring and Kitasato it was thought to be certain that the poison was destroyed by its mixture with the antitoxin, even in spite of certain experiments of Buchner, but the discovery of the preventive action of the serum of animals immunized in affections in which it was impossible to suggest the antitoxic action has certainly weakened or confused this settled conception. It would appear as if the substances themselves were not neutralized, but merely their physiological action; in fact, when the mixture of one part of serum and of nine parts of toxin does not produce, when injected under a guinea-pig's skin, any local or general reaction, it will, when injected into the cellular tissue of the rabbit, produce a well-marked œdema, and may even cause the death of the animal if injected into the veins; the poison, therefore, still remains active, but the serum, leaving the toxin intact, renders the cells of the organism resistant to its action. Roux and Martin found that guinea-pigs in apparently perfect health, which had been some weeks before inoculated against cholera, or with the bacillus prodigiosus, or with the bacillus of Kiel, died no later than the controls after inoculation of the diphtheria bacillus or its toxin, and this in spite of large doses of serum. It may therefore be deduced from these facts that the serum acts upon the organism itself, a very varying factor, and not upon the toxin. That this action upon the organism is manifest by an increase of the phagocytic activity, Gabritchewsky has attempted to prove by studies upon the varying conditions of leucocytosis, and his conclusions are that the influence of the serum makes itself felt on the cells of the organism, and especially upon the phagocytes whose activity and protecting rôle it develops by making them less sensitive to the hurtful action of the bacterium or of its toxins.

Serum Treatment in Poisoning by Vegetable Toxalbumins, and the Venoms of Serpents.

The use of the serum of immunized persons has not been limited to the infectious diseases only, but attempts have also been made to carry out such experiments as against the toxalbumins of vegetables and the venoms of serpents. One of the best arguments in favor of the antitoxic theory of the fluids of the blood is without question furnished by the researches of Ehrlich on the action of the blood serum of animals immunized against certain vegetable poisons. The substance experimented upon belonged to a special category, and cer-

tainly resembled albuminoid materials, such, for example, as the experiments with abrine obtained from jequirity, and ricine. Ehrlich showed that animals which received less than fatal doses of these poisons became very rapidly accustomed to them, and they soon could withstand enormous doses without presenting any symptoms, and he also discovered that if their serum were mixed with these vegetable toxins the latter could be injected without inconvenience in fresh animals. He therefore concluded that the blood of immunized animals possessed the property of destroying these poisons, and generalizing these experiments so as to include the bacterial poisons, following the researches of Behring, Kitasato, and Wassermann, he formulated a theory according to which this immunity was attributed to the neutralization of the bacterial toxins by the fluids of the body. These researches, according to the French, would deserve more attention, were it not possible to establish a complete analogy between them and the recent experiments made in France regarding the venom of serpents. The similarity which exists between the venoms and the bacterial poisons is even more striking than that between the latter and the vegetable toxalbumins of Ehrlich, for we find the same obscurity as to their chemical constitution, the same intensity of action in minute doses, the same secretory origin of living bodies attempting to prepare for themselves some food, and the very great analogy in the symptoms produced. This is more than is necessary in order to suppose the existence between the action of these substances of a very slight line of demarcation.

The Venoms and Antivenomous Immunization.

The researches of Calmette and of Phisalix and Bertrand have shown that it is possible to render a guinea-pig completely immune to the venom of serpents. Phisalix and Bertrand have especially studied the venom of the viper, and have found that this substance, modified by heating for five minutes to a temperature of 80°, possessed immunizing properties. Calmette, using the venom of the cobra, did not obtain as good results by using heat for attenuation. He preferred to inoculate very small doses of active venom, increasing them little by little in a way to obtain a progressive immunity; but the method that he considers the best is closely allied to that of Roux and Vaillard in tetanus and diphtheria. This consists in the diminution of the activity of the poison by the addition of a chemical substance; but instead of using iodine, Calmette preferred the hypochlorites of sodium or calcium, in very dilute solution, one part in sixty. The mixture of this substance with the venom makes it almost

harmless, and enables the animal to withstand an amount that it is possible to increase more and more, while diminishing the dose of the hypochlorite. Calmette showed that this latter substance injected in small quantities in animals for four or five consecutive days could of itself produce the refractory condition.

Antivenomous Serum.—The serum of animals immunized against the venoms possesses very distinct immunizing properties. A mixture of 1 mgm. of the venom of the cobra, or 4 mgm. of the venom of the viper, with a small quantity of the serum of an immunized rabbit can be inoculated in a fresh rabbit without the latter showing any disturbance. The injection into the peritoneum or under the skin of a fresh rabbit, of 3 or 4 c.c. of serum from a strongly immunized rabbit enables the animal to withstand without trouble the inoculation of twice the fatal dose of the venom. Besides these preventive properties, the blood of immunized animals also possesses a very marked curative power, as is shown by the following experiment by Calmette: Suppose a rabbit to be inoculated with twice the fatal dose of a venom that would kill the control in less than three hours; an hour, or even an hour and a half later, the symptoms of poisoning begin; these are regurgitation, acceleration of the heart's action, slight dyspnœa, and paresis of the extremities. After the injection in the peritoneum or under the skin in different parts of the body, of 6 or 8 c.c. of the immunizing serum, the animal will remain a greater or less length of time in a condition of alarming malaise, characterized sometimes by a slight rise of temperature, sometimes by a very marked one. The temperature remains elevated for forty-eight hours, and then gradually returns to the normal. All symptoms then disappear, and if the serum of this rabbit be tested, it will be found that it possesses preventive and antitoxic properties. This power of the serum is not, however, in direct accord with the degree of immunity of the animal.

As may be seen, the identity is complete between the venoms and bacterial poisons, so far as concerns immunity and the immunizing power of the serum, but beyond this, the special properties of the venom have made it possible to make clear many facts of the highest importance from the point of view of the method of action of antitoxins. It has for a long time been debated whether these antitoxins do not act upon the toxins by forming with them a sort of chemical combination, neutralizing them, so to speak, by saturation. The extremely similar properties of these two substances make the problem a difficult one to solve, for the toxins and the antitoxins of tetanus and of diphtheria behave in the same way in the presence of various agents and reactions. It is not the same with the venoms, which are more resisting than these different bodies to the influence of heat, and it

has been possible by heating to 70° to make clear the toxic properties of the venom in a harmless mixture of venom and antivenomous serum. At this temperature the antitoxin is altered and the venom is not, and the heat acts upon the mixture of the two as if each one was alone. It would appear then, that, as a rule, the venom remains intact by the side of the antitoxin, or at least that it is in a very unstable union with it. The study of the antivenomous serum has also given interesting results so far as the special nature of this preventive and curative property is concerned. It is admitted that such serum acts only upon a definite toxin. Antitetanus serum is wholly inefficacious in diphtheria, but, as concerns the venom of serpents, Calmette has shown that the serum of an animal immunized against the venom of the cobra or of the viper acts indifferently upon all the other venoms, that of the naja, the holocephalus, the pseudechis, etc. This interesting fact by itself would be of little importance from the point of view of the analogy already suggested between the different venoms, but Calmette in experimenting upon the action of the venoms upon other immunizing serums showed that the blood of animals vaccinated against tetanus and rabies had also the power to make the venom with which it was mixed harmless, but the reverse proposition was not true, that the antivenomous serum was able to preserve an animal from the toxic action of the poison of tetanus. From this is apparent the complexity of these orrhotherapeutic phenomena, which are but poorly explained by the hypothesis of a chemical action. It is much more probable that the powerful action of the antitetanus or antirabies serum results in making, for a time at least, the cells of the tissues insensitive to the venoms. Besides these interesting theoretical acquisitions, the researches upon the venoms furnish very practical results. Although death by serpent bites is rare in France, it is very frequent in other countries, especially in India, where, according to the statistics, at least twenty-two thousand persons a year die from the bites of these animals. The serum of immunized animals furnishes a rational treatment of unquestionable efficacy, for it has been found that animals can be cured by using this material as late as an hour and a half after the inoculation of the venom. Recent reports from India seem to show a remarkable success in the application of this method to human beings.

Characteristics of the Immunity Due to Serum.

The injection of the serum does not produce of itself any particular phenomena. A most important characteristic of the immunization of the serum is the rapidity of its action. Immediately after the

introduction of the serum, and its diffusion through the organism, the animal, without presenting the slightest symptom, passes from the susceptible to the refractory condition, and will then resist the action of the virus to which it showed itself some moments before entirely susceptible. But the immunity thus produced is essentially fleeting; some days after the procedure the refractory condition disappears, and susceptibility again occurs. The duration and the intensity of the immunity obtained by the injection of the serum are directly proportional to the quantity of the serum introduced and to the degree of its preventive power. It therefore appears as if it were to the persistence in the blood of the therapeutic agent itself that this immunity is due, since the latter appears at the time of the introduction of the agent and disappears when its elimination or destruction is complete. In certain cases, however, the modification of the organism appears to be more profound and more stable. This, at least, is what appears in the results of Fraenkel and Sobernheim regarding the preventive power of the anticholeraic serum, which is a little different from the type of other immunizing serums. According to their experiments, a guinea-pig which has received 2 c.c. of preventive serum can itself furnish, without having been inoculated with the cholera spirillum, a preventive serum of which 2 c.c. is enough to immunize another guinea-pig, and the latter can in its turn become a source of immunizing serum, but after the third generation, this power becomes weaker and disappears. The same authors direct attention to another curious fact which seems to point to a profound modification of the animal organization by the action of the preventive serum. If the serum of a guinea-pig vaccinated against cholera be heated to 70° C., the preventive power persists, but the bactericidal property acquired by the immunization is destroyed; nevertheless, if this serum, which is not bactericidal, but is preventive, be injected into another guinea-pig, there is produced in this animal a serum possessing the two properties, apparently produced by the heated serum. The methods of immunizing are of two general classes, namely, the inoculation of living bacteria, and the injection of their soluble products. Whether the one or the other be used, the immunity produced differs absolutely from that obtained by the use of serum, showing that immunity is not a fixed and absolute biological property, but that on the contrary, variability and relativity are a part of its very essence. Toxin immunity is dangerous and difficult to obtain, but its results are very lasting. Serum, or antitoxin immunity is safe and easy to obtain, but its results are very fleeting. Practically, the serum or antitoxin immunity is the only one that we are justified in applying to the human race.

The Active Element of the Serum.

The analogies existing between the genesis and the effect of the preventive serum in different affections leads to the question as to what is the common quality that unites them, and what is the cause. There is no doubt that there exists in these different serums an element to which the preventive power must be ascribed. It is generally admitted that this element is a definite chemical substance, to which has been given the names of antitoxin and stimulin, but the names themselves summarize practically all that is precisely known of the nature of this substance which has so intense a biological action. Attempts to concentrate or isolate it have not been successful; on the one hand, experiments have shown that if the globulin of the serum be precipitated, the albuminoid material that remains behind is entirely inactive, and, on the other hand, Aronson claims to have obtained an albuminoid material a hundred times more active than the diphtheritic serum used in its preparation, without any pretense, however, of obtaining the antitoxin in a condition of purity; in fact, the discussion upon the antitoxins is of the same nature as that upon the bacterial toxins, and neither of them is concluded.

The Origin of the Active Element.—Whatever the chemical nature of the active substance may be, research as to its origin and method of formation should be carried on. One of the very first hypotheses was that of Emmerich, who believed that the antitoxin was the result of the combination of the toxin with certain albuminoid materials of the blood, to which complex compound he gave the name of immunotoxprotein. If it is certain that the existence of the preventive property is due to the introduction of bacterial products in the organism, the hypothesis of Emmerich fails in view of the fact, observed by Roux and Vaillard in animals immunized against tetanus, that it is possible by successive bleedings to take away a quantity of blood equal to the entire mass of this fluid, without the antitoxic power being noticeably diminished, and this without a fresh introduction of toxin; this shows very clearly that the toxin does not produce antitoxin directly by a transformation or an organic combination. If it is not possible to seek for the effective origin of antitoxin outside of the economy, it must be admitted, whatever its nature, that it is formed by the organism in all its parts, and results from the putting in activity of vital functions by definite agents of the nature of pathogenic bacteria or their culture products. It is difficult to go further than this without entering the region of hypothesis. The preponderating presence of the antitoxin in the blood makes the exact determination of the

mechanism of its production a difficult matter. It is difficult also to admit a direct modification of the fluids, and the most active partisans of the humoral theory are inclined to concede that this action of the serum is due to the activity of certain cells; they even seek to establish by this concession a sort of compromise between the humoralists and the partisans of the cellular theories; and in support of this hypothesis may be cited the interesting observation of F. Klemperer, that the yolk of an egg of an immune chicken was antitoxic while the white was not; but if this opinion be accepted, the solution is only begun, and the determination of the cellular element that forms the antitoxin in the blood is still to be made.

One line of experiments has been carried out by Hankin and Kanthack, who lay stress upon the action of the eosinophilic leucocytes. They believe that these cells, these alexocytes, for this is the name that they give to the eosinophilic cells which have no direct phagocytic action, secrete certain proteid substances, which they call alexins, whose presence in the fluids exerts a hurtful influence upon the bacteria, disabling them against the polynuclear leucocytes, which are the true phagocytes, and which, therefore, from this point of view occupy only the second line of defence. It is possible also to suppose that the preventive substance is due to an internal secretion. Metchnikoff attempts to destroy this theory, demonstrating that the vaccinations or infections are without any effect upon the number or the activity of these cells, which, on the contrary, play a preponderating part in the pathological histology of certain non-infectious diseases, like leucocythæmia and asthma. He explains the error of interpretation of Hankin and Kanthack by a confusion due to the kind of animal upon which they experimented. In the rabbit, which they used, are found a large number of polynuclear leucocytes, true phagocytes, whose protoplasm contains a large number of granules which in spite of their selectivity for the neutral aniline colors may at first sight be taken for eosinophilic cells, and thus facilitate the error into which all the English experimenters appear to have fallen. But if the eosinophilic cells are out of the question, can the same be said with regard to the other white corpuscles of the blood? Among the known facts, some are in favor and others opposed to this opinion. Among the latter, may be mentioned in the very first place, the absence of any preservative power in pus. It would appear, in fact, if the preventive substance were the product of the activity of polynuclear leucocytes, that it ought to be present in large amount in this liquid where these cells are found in great numbers, but the experiments of Botkin have shown that pus from animals furnishing a very powerful antitetanus serum has itself only very slight antitoxic prop-

erties, and similar observations have been made in other affections. It is especially to the bactericidal power that it has been sought to compare the preventive properties of the serum, and, in spite of the great differences existing between these two biological qualities, it is interesting to recall the observations which seem to assign a leucocytic origin to the bactericidal power. It is known since the work of Behring and Nissen on the vibrio of avian septicæmia, and of Zaslein on the spirillum of cholera, that the serum of animals vaccinated against these bacteria exerts upon them a bactericidal action that is not found in fresh animals, and Pfeiffer has shown that in hypervaccinated animals the blood serum destroys the bacteria almost completely without any phagocytic intervention. From observations of Metchnikoff, it appears that this fact, which it was attempted to use as an objection to the phagocytic theory, on the contrary bears in its favor, if the conditions of digestion in the animal be considered, intracellular in the infusoria, then extracellular, as one ascends the animal series. He suggests then a seductive theory, that an analogous fact explains the objection of Pfeiffer, and if the leucocytes of vaccinated guinea-pigs secrete substances capable of destroying the vibrio, in the hypervaccinated these substances become so abundant that they may escape outside and diffuse in the serum. Whether or not an analogous occurrence takes place as regards the preventive power, only the future will show. As to the secretion of the antitoxin by a definite organ, experiments are negative. Roux and Vaillard, in their experiments upon tetanus, found no organ taking any special predominance, but nevertheless, for various reasons, the spleen and the suprarenal capsules have been thought to play a special rôle in the production of antitoxin. So far as concerns the spleen, the only argument is that of Tizzoni and Cattani, who found that they could not immunize against tetanus animals which had been deprived of their spleen, but this fact, allied to the theory of splenic alexins of Hankin, is deprived of value by Vaillard, who found many animals immunized against tetanus whose splenic pulp possessed no antitoxic power. As to the suprarenal capsules, they have attracted attention especially by analogy. From the experiments of Abelous and Langlois, these organs appear to exercise protection against the organic toxins, the result of muscular activity, and this antitoxic action has been compared to the anatomical fact of the almost hemorrhagic congestion of the suprarenal capsules in the intoxication by the bacterial poisons, especially the toxin of diphtheria, but no positive fact can be brought forward to support this hypothesis.

It seems certain that the blood serum is the organic element that

possesses the preventive power in the highest degree. It is from this that the other fluids of the body appear to have borrowed their power whenever an analogous action has been found. The fluid of œdema, which contains less fibrin than the blood serum, possesses properties equal to those of the latter; the aqueous humor is a little less active; the urine and saliva, although coming from animals very highly immunized, possess the preventive property only in extremely feeble proportions as a rule; and pus has been shown to possess an activity far inferior to that of blood serum. As to milk, the first experiments are those of Ehrlich, who showed that feeding young mice upon the milk of a mouse refractory to the vegetable toxins was sufficient to immunize them. Brieger and Ehrlich later demonstrated the immunizing properties of the milk of animals immunized against many infections, and Roux and Vaillard in their work upon tetanus placed milk immediately after the serum in its protective power. Ketscher showed that the milk of the goat immunized against cholera possessed very marked preventive properties without any bactericidal, and Klemperer and Popoff have corroborated these conclusions with respect to cholera, while Koudrevetski never obtained well-defined results in using the milk of a goat, whose serum possessed, nevertheless, very marked preventive properties in diphtheria. It would seem as if this protective power of the milk was especially an act of deprivation, for the power of the blood serum, other things being equal, diminishes more rapidly in milk-giving females. In spite of the ease with which milk could be used practically, it is doubtful if it would ever supplant serum; but in serious cases its properties might be utilized successfully, especially if we were able to concentrate its power in an alcoholic precipitate which should contain all the active substances, that might be redissolved in a small volume of water. As to the maceration of the splanchnic organs, which appears to have given results with Mosny superior even to serum itself in pneumonic vaccination, this appears to be a method of rather restricted application, and it is probable that in practice, when a choice is offered, some other method would be preferred which would not require the sacrifice of the animal.

Theory of the Protective Action of Serum.

The question arises whether the preventive power is susceptible of being explained by a general theory. Experiment reduces to nothing the confusion between the preventive power and the bactericidal power of certain serums; the latter, which is more or less unstable, being unable to resist a temperature of 60° C., is so inconstant in immu-

nized animals, that it is not possible to consider that it plays a prominent rôle in the production of immunity. It cannot be denied that there is a marked affinity between the preventive and the bactericidal property, as the experiments of Fraenkel and Sobernheim demonstrate in cholera, but the differences are still more marked, the bactericidal property being essentially a contingent property, and the preventive power a vital act of much greater constancy and importance. The theory of the attenuating power in the production of immunity is almost abandoned nowadays, and appears to have been based upon an error of interpretation of the preventive power, and served only to attract attention to the latter. Attempts have also been made to identify the antitoxic with the preventive power, and the wide acceptation of the word "antitoxin" has had no little to do with the spreading of this error, than which nothing could be greater, for the preventive power corresponds to a much more general quality than the antitoxic power, which has thus far been demonstrated only in tetanus and diphtheria. The researches upon hog cholera, typhoid fever, pneumonia, avian septicæmia, and cholera have shown that the serum of immunized animals protects fresh animals against bacteria, but has no action upon their culture products. The preventive power being able to exist without any antitoxic property, it cannot, therefore, be due to the latter that the organism is protected, as the examples of diphtheria or tetanus would lead one to suppose, and, in view of this fact, the question may very properly be asked, whether there really is an antitoxic action, that is to say, whether the serum really does act upon the toxin to make it inoffensive. Direct proof would be difficult. Our want of knowledge of the chemical nature of the tetanus and diphtheria toxins makes it impossible to discover the modifications that they may undergo upon the mixture with immunizing serum. In order to test the qualities of this serum, a living reagent must always be employed, and this introduces a third factor into the problem. The extreme instability of the toxins of diphtheria and of tetanus makes direct experiment impossible, for, in attempting to destroy the antitoxic power of the blood, the toxin itself is also destroyed, but the analogies between these poisons and the venoms of serpents make it possible to apply to them the observation made in regard to the latter, that a mixture of antivenomous blood and of venom, in such a proportion that it is entirely harmless, recovers all its hurtful powers by heating to 70° C. This temperature destroys the antivenomous power of the blood without altering the venom, by which action also is demonstrated the persistence of the latter in the mixture. If the serum acted upon the toxin in such a way, for example, as that one part of serum destroyed one part of

toxin, it would be possible to inject in an animal with impunity an indeterminate quantity of the mixture, providing the proportion of the serum and of the toxin was the same, and sufficient for the neutralization of the latter; but this is not the case, large doses of the mixture always producing a fatal result. The same conclusions are reached if, instead of varying the quantity of the mixture, the resistance of the animal is altered. If the mixture was itself harmless, and the organism passive, all the animals of one species ought to resist in the same way, but they do not. If a mixture of tetanus toxin and of antitetanus serum be injected in a guinea-pig in perfect health, but which has been recently vaccinated against a bacterial disease, such as cholera for example, the animal will succumb to the injection of a quantity of the mixture harmless for a normal guinea-pig; and further, if after the inoculation of the serotoxic mixture the products of bacterial culture be injected, the toxin alone shows itself, an evident proof of the persistence of the tetanus poison in the mixture; so that it would appear simply that the serum does not act directly on the toxin which exists intact and side by side with the protective substance, and this latter exerts its action by bringing into play certain forces of the organism whose absolute integrity is necessary for the manifestation of its influence. The antitoxic action, therefore, does not exist, although this property has been assumed to be the preventive power in diseases in which the serum does not protect the animal economy against the bacterial products. In the two cases, in fact, we have to do with a definite stimulation to the forces of the organism, which would lead to the preference being given to the word "stimulin," originated by Metchnikoff, for the protective substance, instead of antitoxin, which is only confirming an erroneous idea. As to what cells this stimulation is exerted upon, and what are the biological bacterial phenomena which give it sequence, the French assert that it is especially the phagocytes, the increase in number of which is the first effect of the irritation exerted by the stimulins. In the greater number of infections there occurs an actual leucocytosis by the considerable increase of the proportionate number of the polynuclear leucocytes, but this is not absolute, and in general leucocytosis does not occur in cases in which the parasite remains strictly limited to the site of the local lesion. The experiments of Gabritchewsky concerning the part played by the leucocytes in diphtheria infection show that in this disease general leucocytosis is unfavorable. One of the first effects of the injection of the curative serum is to diminish the number of the leucocytes, yet a study of the local lesion would lead us to diametrically opposite conclusions. While a great number of free bacilli and the generated leucocytes are found

in a fresh animal that has received the serum, the bacteria are, on the contrary, all englobed in the numerous phagocytes that form a living barrier to the bacterial invasion. Thus, under the influence of the stimulation, the leucocytes appear much more numerous at the point of insertion of the bacteria, and especially resistant to the necrotic action of the toxin which enables them to englobe the bacilli instead of yielding to the poison which they secrete. In addition to this increase of number and resistance, it also appears that under the influence of serum the zymotic action of the leucocytes increases; thus Gabritchewsky has seen that under a proteolytic action certainly due to the leucocytes the false membrane becomes much more rapidly detached in animals treated by the serum than in fresh guinea-pigs. This phenomenon can be compared to that occurring in guinea-pigs hyperimmunized to cholera, whose serum exerts upon the bacteria an actual solvent action, so that many observations appear to establish that the serum acts by stimulating the activity of the leucocytes, and enabling them more easily to englobe and destroy the bacteria. The most curious part of this action certainly is its specific nature, each serum exciting the leucocytes only against a special variety of bacterium; nevertheless, if the serum of an animal vaccinated against a definite affection exerts a selective influence, it would be possible to obtain analogous results by stimulating the phagocytes by other non-specific substances which should give analogous results, although perhaps less intense. Issaeff, experimenting with the serum of cholera, saw that the phagocytes englobed the vibrios with an unusual vigor after a simple injection of tuberculin, which observation may be compared with that supported by Calmette, that the simple injection of hypochlorite of sodium is sufficient to develop in an animal the antivenomous power, but this latter property would seem to be a little less selective than that acting against the bacterial toxins; in fact, antitetanus serum exerts upon the venoms an action analogous to that of the serum of animals made refractory to the venoms, although the converse is not true, and the antivenomous serum has no action on a tetanus toxin. This antivenomous action of the serum raises a question of great interest. If we believe that the preventive action of the serum resides in phagocytic activity, the englobing and the destruction of the bacteria being made more easy and more rapid, it may be asked if it is not by an analogous mechanism that it protects the organism against special bacterial toxins. It has been shown that there is a great difference between the different types of the bacterial poisons, and that the organism reacts in an entirely different way to the toxins of diphtheria and tetanus than to the products of other bacteria. These two, in fact, form a class apart, and the economy attempts

to act towards them as it does towards living bacteria. Recent experiments appear to show that this protective action is also due to the leucocytes. The researches of Chatenay have demonstrated that in animals poisoned with one of these toxins, or with a vegetable toxalbumin, or a serpent venom, the leucocytic phenomena are entirely comparable to those observed in the infections. There is produced a marked hypoleucocytosis, if the animal is susceptible, and death is rapid. Many of the leucocytes increase, on the other hand, when there is a long or successful resistance; furthermore, the leucocytic action does not appear to be limited to this special form of poisons, and Metchnikoff has observed absolutely analogous facts in animals poisoned with arsenious acid; but there is a hyperleucocytosis, on the other hand, in those in which a progressive use has produced a refractory condition. The study of this protective action of the phagocytes against soluble poisons is extremely interesting. The experiments of Kobert, Stender, Samoiloff, and Lipski, upon the absorption by the leucocytes and endothelial cells of iron and silver in solution appear to establish that the phagocytes are able to extract certain soluble bodies from the medium in which they are, and to retain these bodies in their protoplasm, thus making them harmless for the other cells of the economy. These facts should not produce surprise, for the electivity of the cells and even of their different constituent parts is too well known, since it is upon this property that all the technique of staining is based; for example, a section placed in a weak coloring solution of hæmatoxylon after a certain time stains itself intensely by absorbing almost the whole of the coloring substance in solution in the fluid, and it is only reasonable to suppose that the living cell has as great a selective power as the dead. As to the mechanism by which the intracellular destruction of the absorbed toxins occurs, a theory may easily be built up. It is known that the animal diastases, such as pepsin or trypsin, rapidly destroy the tetanus or diphtheria toxin, and it is probable that this destruction is a result of the phenomena of intracellular digestion. These facts show well the increasing importance of the rôle of the phagocytes in the protection of the organism, so that it is easy to understand how powerful stimulation exerted by the serum upon these defenders may produce in so short a time results of such great importance.

Nature of the Germicidal Constituent of the Blood Serum.

Vaughan and McClintock reach the conclusion, first, that the serum albumin is not the germicidal substance in blood serum, for Buchner has demonstrated that the germicidal action is not destroyed

after subjection of the liquid to the action of pepsin; second, that the germicidal substance is probably a proteid, or it would be difficult to explain why a temperature of 55° destroys its activity; third, the only proteid likely to be present in blood serum which is not destroyed by digestion is nuclein. They then attempt to determine, first, whether there is a nuclein in blood serum, and second, whether if so, it has germicidal properties. Both of these points they seem to have settled. Blood serum of dogs was taken, and to it was added five volumes of absolute alcohol and five of ether. The white precipitate resulting was allowed to stand several hours under the mixture of alcohol and ether, which was frequently changed, and finally removed. The precipitate was then subjected to the action of pepsin in the presence of hydrochloric acid until no further digestion would take place. The undigested residue was collected, washed first with dilute hydrochloric acid, and then with alcohol, and finally dissolved in caustic-potash solution, 0.12 per cent., containing 0.6 per cent. of sodium chloride. This solution was sterilized by filtration, and gave the reactions of nuclein. Experiments with this liquid seem to show that it has great germicidal power, as instanced by its effect on cholera spirillum, staphylococcus pyogenes aureus, and non-spore-bearing anthrax. The germicidal power is destroyed by heat, but not so readily as might be supposed. Vaughan further says that there seems to be no doubt that the nuclein formed in organs of the body is mostly concerned in the production of immunity. The nuclein formed by these cells, or in the organs, passes into the blood, partly in solution, and partly in the form of multinuclear white corpuscles, the so-called phagocytes. He believes that the nuclein passes from the cell into solution, but is unable to say whether this process is due to the breaking down of the cell or to an active secretion on the part of the cell. The action of the soluble or alkaline nuclein on bacteria might be either inhibitory, or directly toxic, or both. It is not necessary that the invading microörganism be killed in order to prevent its producing disease. There are three facts observed in the production of immunity in an animal naturally susceptible: there must be first an inhibiting or immunizing substance introduced into the body; secondly, the organs whose activity is stimulated by these immunizing agents are those which elaborate nuclein, such as the spleen, the thyroid glands, and the bone marrow; thirdly, the antidotal substances are a form of nuclein. The kind and amount of nuclein found depends upon the nature of the inciting agent, and the condition of the organ or organs acted upon. The word "nuclein" is used in the broad sense, including the nuclein acids and nucleoalbumins.

Since, then, we have learned that the animal body itself generates a germicide more powerful than corrosive sublimate, and since we know how to increase this substance in the blood, and can isolate it and inject it into other animals, the therapeutic prospects for the future are very bright.

The Hereditary Transmission of Immunity.

Gley and Charrin in their experiments upon this subject injected toxins into the mother and father, sometimes into one only, sometimes into both. In many of these conditions they observed transmission of the immunity, but it was always rare and incomplete, especially when only one of the parents was immunized, and particularly when this one was the father. In this case the transmission is wholly exceptional, and to demonstrate it at all very long and numerous experiments, extending over years, are necessary, a great obstacle to which is the frequency of abortions, rapid death, or sterility.

WATER-BORNE DISEASES.

BY

ERNEST HART

AND

SOLOMON C. SMITH,

LONDON.

WATER-BORNE DISEASES.

INTRODUCTION.

THE various forms of disease-producing contamination to which water is subject may be divided into two main groups, according as the contaminating substance is living or non-living. The importance of this distinction hinges largely on the fact that dilution of a non-living poison proportionately lessens its injurious qualities, whereas this is not always the case in regard to the contamination of water with living organisms, their power of rapid multiplication neutralizing to a considerable extent the influence of dilution.

DISEASES CAUSED BY NON-LIVING MATTER.

The non-living impurities which we have to consider are lead; in a minor degree zinc, arsenic, copper, and iron; clay and marl; excessive amounts of lime and magnesian salts; and various organic products arising from the decomposition of animal and vegetable substances.

Plumbism.

Lead poisoning from the use of drinking-water often takes on the typical form of a water epidemic; that is, it occurs among a considerable number of people at the same time, or in rapid succession, within an area having a single source of water supply, while those living outside that area remain unaffected. In such cases it usually arises from the water of a public supply being, or, as is often the case, becoming temporarily capable of dissolving the lead in the service pipes or cisterns. But lead poisoning may also occur sporadically and yet be a truly water-borne disease, the poisonous quality of the water arising from some local peculiarity in its mode of distribution or its use—such as its having to pass through an inordinately long pipe on its way to the house in question, or from the habit of using for dietetic purposes water from a hot-water circulation, the pipes of which and even perhaps the cistern are made of lead, for often it may happen that a condition of water which would

not suffice to dissolve an appreciable quantity of lead under the ordinary circumstances of its distribution, may under such exceptional arrangements become impregnated with so large an amount of the metal as to become deleterious. A matter of great interest and importance in regard to water-borne plumbism is the fact that a water supply which at one time may appear entirely devoid of the power of acting upon lead may at another time possess this evil property in a marked degree; so that it becomes important to know not only whether a given water is at the moment of examination capable or incapable of dissolving lead, but also whether it is or is not of such a class as is shown by experience to be liable at times to develop this plumbo-solvent power.

The nature of the substance by virtue of which water acquires the property of dissolving lead has not yet been satisfactorily determined, and in fact according to modern views that is not exactly the form the question really takes, for when it is recognized that the purest water possesses this power, it becomes obvious that what has to be determined is rather, What is it that so generally prevents water from exercising its natural power of dissolving lead? than, What is it that enables it sometimes to act upon this substance? In any case what is clear is that waters drawn from apparently similar sources vary greatly in plumbo-solvent power, and that even water drawn from the same source may alter much from time to time in its activity in that direction.

Generally it may be stated that soft moorland waters, containing, as they often do, a certain amount of acid, are the most dangerous, and that those containing alkaline carbonates, especially calcic carbonate, are the least so; but it is to be noted that in some cases waters which at their source and in the great containing reservoirs act vigorously upon lead may, as in the case of the water supplied to Glasgow from Loch Katrine, be found, by the time they have arrived at their place of distribution, to have but a very insignificant action on lead pipes.

The great variability in the plumbo-solvent action of waters known to possess that property, and the fact that these waters are so commonly derived from open moorlands where vegetable life is active, while spring water rarely possesses the same property, led Mr. W. H. Power to question whether "the seemingly inscrutable behavior" of soft moorland waters in regard of plumbo-solvent ability might not be related to the agency, direct or indirect, of low forms of organic life, and this question has since been investigated by Prof. W. R. Smith, but without any definite results.

That moorland water often possesses acidity is well known, but

the nature of the acid is open to some doubt. It has been stated to be of vegetable origin and has been described as humic or ulmic acid; carbonic acid is certainly often present, and there is much reason to believe that nitric acid also frequently exists in soft moorland waters. There is, however, but little reason to believe that any of these acids directly combine in any large quantity with lead. It has been shown by Garrett that even distilled water acts upon lead, the first step being the formation of an oxyhydrate. This action is greatly facilitated by, even if it be not entirely due to, the presence of some form of oxide of nitrogen which acts as a carrier of oxygen, giving this up to the lead and then becoming re-oxidized in the presence of air, the same small quantity of nitrogen being used over and over again.

The oxyhydrate of lead produced in this manner is freely soluble in acids, as also, though in less degree, in solutions of various salts. The power which certain waters have of taking up lead into solution is thus easily explained. The acid may be so feeble that of itself it may have but little solvent power, but if in addition the water contain an oxide of nitrogen, a "carrier" of oxygen, an intermediary by which oxide of lead is produced, this latter oxide will combine with the acids which may be present, and thus soluble salts of lead will be formed. It is also to be observed that if the water contain salts of other bases the oxide of lead may decompose them and thus, in a secondary manner, become dissolved, although a non-acid water is never likely to contain as much lead in solution as a water which is originally acid. It must not, however, be imagined that lead poisoning by means of water is always due to lead which has become dissolved. The mere oxidation of lead takes place most rapidly in neutral or very slightly alkaline water, and in such water the oxide so formed does not dissolve. But if such oxidation has been going on in a service pipe during the night, or during a time when no water has been drawn, the solid lead hydrate will be swept out by the stream when the tap is turned, and the oxide so suspended in the water will act as a poison to those who partake of the first draught just as surely as if it had been in solution.

The waters which do not dissolve lead are those which contain alkaline carbonates and especially calcic carbonate. It seems to be the presence of these carbonates, and especially of carbonate of lime, which protects lead from the solvent action of ordinary water, and with this knowledge it is not difficult to understand that water flowing from peaty moorland, where on the one hand it becomes charged with acids arising from decomposition of organic matter, and on the other has but little chance of meeting with lime salts, should possess in a high degree the power of dissolving lead; nor is it difficult to

understand how, as the result of variations in the rapidity of rainfall, and thus of the amount of alkaline carbonates contained in the water, its oxidizing power may vary greatly; while, on the other hand, according to variations in temperature and in other conditions favoring the production of those acids on which the plumbo-solvent power of the water so largely depends, a water which is usually innocuous may under certain circumstances, at present ill defined, become charged with lead.

The result of both chemical research and practical experience is to show that the best method by which a soft and lead-solvent water can be rendered safe is either to let it flow over a sufficient area of chalk or limestone to impregnate it with a due allowance of calcic carbonate, or to mix with it a quantity of powdered chalk sufficient to produce the same effect.

The *modus operandi* is probably twofold: on the one hand the lime salts neutralize the acidity of the water; on the other they turn any such oxyhydrate of lead as may be formed into a carbonate, which is practically insoluble unless the water contains a considerable excess of carbonic acid, and it is found that when the pipes are once coated with this protective lining of lead carbonate a very small amount of calcic carbonate in the water is sufficient to prevent any further action upon them.

Waters which do not dissolve lead owe their innocence in this respect largely to their power of forming a protective coating on the lead consisting of salts which are insoluble in the particular water in question. In the case of many waters which contain calcic carbonate or carbonic acid this coating consists of lead carbonate, which is difficult of solution unless the water contain a considerable excess of carbonic acid under pressure; but in other waters crusts are formed composed of mixtures of carbonates and sulphates of lead, lime, and magnesia and of chloride of lead, as the case may be.

For the artificial production of a protective coating the amount of lime or chalk added to the water need not be large, and if the amount be properly regulated the utility of the water for purposes of washing is not materially lessened, while for dietetic purposes it is probable that the addition of a modicum of lime is really an improvement.

A word must be said as to the selective power of lead in regard to the persons whom it attacks, and also as to the means to be adopted when it is known that the water used is capable of dissolving lead.

The connection of plumbism with gout, as also with renal disease, is well known, but it is worth remembering that it is probable that

in regard both to gout and renal disease it is the same defective eliminative capacity of the individual, which leads to these disorders, which also makes lead poisoning show its effects so readily upon those who suffer from them.

Wherever soft water is used it is necessary to be constantly on the *qui vive* for lead poisoning as a possible cause for constipation, dyspepsia, neuralgia, neuritis, and various forms of nerve degeneration, especially when they occur in people of gouty proclivities. The treatment of such conditions does not fall within the province of this article, but in regard to prevention it is worth while to remember that a good charcoal filter, the charcoal of which is frequently renewed, will entirely remove lead from water, that the most poisonous water is that which has been lying for a considerable time in the pipes and notably the first drawn in the morning, and that the use of water from a hot-water circulating arrangement for dietetic purposes is a fertile cause of poisoning by lead. It is no uncommon thing to find that the one member of the family who rises early and has something warm before going to his work, is the one member of the family who suffers. Sometimes he gets the first draw from the pipes in which the water has been standing all night; sometimes, to make the kettle boil more quickly, it has been filled from the hot-water tap, and in either case with the same result, namely, a dose of lead.

Poisoning by Zinc, Copper, or Arsenic.

In practice these metals are hardly ever found in water except as the result of its contamination with the products of trade processes. The presence of any of these metals is injurious and renders waters unfit for dietetic purposes. Zinc may sometimes be found as the result of the action of water upon cisterns, but this would hardly occur except in the presence of such an amount of organic matter, or nitrites and nitrates, as should itself render the water open to suspicion.

Dyspepsia, Diarrhœa, and Ptomain Poisoning.

Certain disorders of the digestive organs which all declare themselves ultimately by the development of dyspepsia are apt to arise from the use of water containing an excess of calcium sulphate, calcium chloride, and the magnesian salts. Water derived from the red sandstones and magnesian limestones of the permian and triassic systems are especially apt to have this effect; and it has been found in several instances that the substitution of a soft for a hard water supply in large towns, as for example, in Glasgow, has had the effect

of much lessening the prevalence of dyspeptic complaints. The presence of iron also may give rise to headache and constipation.

Such forms of diarrhœa as may be presumed to arise from the toxic products of microbic life will be referred to later, but it must be mentioned here that such suspended mineral matters as marl and clay, which exist largely at certain times of the year in the Mississippi, the Ganges, and other rivers, are said to be capable of producing diarrhœa; while there can be no doubt that suspended and dissolved organic matter, especially if arising from fecal contamination as in cases where water has been polluted with sewage, may give rise to very severe diarrhœa independent of any specific action by definite pathogenic microbes. Many instances could be adduced in which epidemic or endemic diarrhœa has been associated with pollution of the water by products of decomposition of either animal or vegetable substances, and in which the disease has disappeared on the substitution of a purer supply of water.

The water derived from graveyards seems to be especially hurtful in this respect. It seems quite clear also that water which has absorbed hydrogen sulphide arising from decomposing matters, or certain as yet ill-defined vapors which are spoken of as "sewer gases," may give rise to diarrhœa and a distressing sense of malaise. What is the deleterious material in such cases is far from clear; the whole subject of sewer air and its noxious influence is in fact involved in considerable obscurity. We have on the one hand the assertions of many who, after investigating the matter chemically and bacteriologically, affirm that the air of sewers contains but few micro-organisms, at any rate fewer than exist in the outside air at the same time, and that as regards carbonic acid, organic matter, and micro-organisms the air of sewers is, quantitatively, very much better than that of naturally ventilated schools. According to Drs. Connelly and Haldane, "sewer air contained a much smaller number of micro-organisms than the air in any class of house they had investigated," and Parry Laws, in his report to the London County Council in 1892, showed that the micro-organisms in the sewer air were related to those in the air outside and not to those in the sewage.

On the other hand we have a very large clinical experience pointing definitely to the baleful influence of sewer air when admitted into dwelling-houses. In our opinion there need be no hesitation in admitting that much disease of an indefinite type—malaise, headache, anorexia, and debility—is caused by the entry into houses of sewer air, which besides producing these evils certainly so lowers the vitality of those exposed to its effects as to render them more prone than others to various pathogenic influences. It is to be noted

that sewer air pretty uniformly contains more "organic matter" than the air outside, while of the exact character of this "organic matter" very little is known. In this organic matter doubtless lies the cause of the evil consequences of sewer air. In view of what we know, then, as to the small quantities of various ptomains by which poisonous effects can be produced, it seems not unreasonable to attribute sewer-air poisoning to the effect of analogous products of decomposition, and to regard in the same light the undoubtedly injurious effects produced by the ingestion of water which has been exposed to such exhalations.

DISEASES CAUSED BY LIVING ORGANISMS.

We now come to the consideration of those diseases which depend on the ingestion of specific germs or living organisms. It will be noticed that we here enter upon a new phase of the subject. Hitherto we have dealt with maladies which are produced by certain poisons which, whether merely mineral or the organic products of preceding life, are at least entirely devoid of life themselves. We have now, however, to consider diseases which are caused by living matter, germs planted in man and growing in his organs or tissues. Such disease-producing or pathogenic organisms are of many kinds. Some are exotics, occasionally growing in man but normally quite independent of him; others are normally parasitic upon man, but can for a time maintain a separate existence; others again are exclusively parasitic and are not known to grow except in human soil. The life history of these organisms also varies greatly. The growth of some is a mere repetition, generation after generation, of the same form; in other cases one phase of life is gone through within man and another quite different one outside; while in others the outside phase may require the presence of another animal by whose aid alone the cycle can be completed. Again, as regards the water-carriage of these diseases, in some the water acts merely as a carrier, while in others the germs of the disease can multiply within the water in which they float. These points are not mentioned here with a view of establishing any sort of classification, but to show how little it is possible in such a matter to trust with any degree of safety to analogy in the interpretation of the phenomena of the various diseases in question. The temptation is no doubt often strong to interpret the unknown in regard to one disease by what is known in regard to another apparently analogous condition, but a consideration of the very varying life histories of the different micro-organisms on which these diseases depend shows how unsafe a course this must always be, and how necessary it is to work out independently the history of each malady.

The Entozoa.

We shall take first the grosser forms of parasitic life which are provocative of disease.

Tape-Worms.

The eggs and the embryos of certain entozoa exist in water, and thus the maladies which they set up must be counted among the water-borne diseases. The various forms of tænia pass through their alternate phases of life in the bodies of different animals; existing in the flesh of one in the form of a cysticercus and in the intestines of other in the form of a worm. Thus the tænia solium exists as a tape-worm in a man, while its cysticercus form infests the pig. The cysticercus of the tænia mediocanellata, on the other hand, is found in the flesh of the ox, and it is manifest that in neither of these cases is the interposition of water necessary to carry the ova from man to the intermediate host. In regard to the bothryocephalus latus, however, the matter is somewhat different. The intermediate host is a fish, and the embryo is an actively moving ciliated body which is capable of living for several days in water. Both eggs and embryos are found in river water, from which they are swallowed by fishes, pikes, eel-pouts, etc., in whose muscles they take on the form of cysticerci; and it is no doubt from the eating of such fishes in an imperfectly cooked condition that man becomes infested with the corresponding form of worm.

There is, then, this peculiarity about the rôle played by water in the dissemination of the bothryocephalus latus, that this is not directly carried to man by water, but that water is necessary for the transport of its eggs to fishes in which it passes its intermediate phase of existence.

Round-Worms (Ascaris Lumbricoides).

Water may also become the vehicle by which the eggs of various round-worms may be distributed. It seems somewhat uncertain whether the eggs of the ascaris lumbricoides are capable of producing the worm without some intermediate as yet unknown phase of life. Instances, however, are on record of outbreaks of what one might almost call epidemics of the ascaris lumbricoides, which could not be traced to anything in common except the use of drinking-water from shallow wells which was greatly contaminated by substances washed in during excessive floods.

Ankylostomum Duodenale.

In regard to the ankylostomum duodenale it is well known that the workmen in certain mines and tunnels have been infected by means of water containing its eggs, although in the countries where it is endemic it is generally considered that damp earth, rather than water, is the medium by which it is carried to the hands and thus to the mouth of those who are attacked by it.

Oxyuris Vermicularis.

The oxyuris vermicularis is certainly communicable in drinking-water, although that is not its usual mode of transfer.

The chief interest which civilized, town-dwelling man has in the water-carriage of these parasites is in regard to sewage farms. Although statistical proof is unattainable, it is difficult to avoid a strong suspicion that in many cases uncooked vegetables such as lettuce, cress, and other varieties of salad must be liable to transmit these entozoa from person to person when they are grown on soil which is enriched by a form of manure so likely to contain the eggs of these creatures.

In places, however, where the water supply is derived from shallow wells and running streams which are liable to be polluted with the washings of agricultural land which has been manured with human excrement, these various forms of round-worm are probably very frequently water-borne.

Dracunculus Persarum.

The dracunculus persarum, or guinea-worm, has a curious life history. In man it is known as a worm growing under the skin of the legs and feet and other exposed parts. It had long been thought that it gained access to these parts directly during bathing or wading in water which contained its embryos. The opinion, however, has lately gained ground that the relation is a more complicated one, involving the interposition of an intermediate host; the embryo entering the body of a cyclops, a common inhabitant of water, in which it undergoes one stage of its development, and only then becoming fitted for its further phase of life as a parasite of man. The water containing the cyclops is swallowed; the contained embryo makes its way to the surface of the body, where it lays its eggs under the skin. The relation of bathing, wading, etc., to the development is thus connected rather with the giving out of the eggs to the water than to their absorption by the skin.

Filaria Sanguinis Hominis.

The filaria sanguinis hominis is another worm which requires two animals in which to complete the cycle of its life, and it also requires water as a vehicle from one animal to another. The disease produced by the filaria sanguinis is, however, more truly water-borne than that produced by the guinea-worm, in that it is the final transit from the intermediate host to man that is effected by water.

In man the filaria parasite inhabits the lymphatics and the blood-vessels. The female parent worm is found inhabiting dilated lymphatic vessels, where it discharges an enormous number of ova which are sufficiently small to pass into the thoracic duct and thus to gain access to the blood-vessels, in which they are often to be found in immense multitudes.

We need here only mention the curious fact that these embryo filariæ can be found in the blood-vessels of the skin only during the night. Probably during the day they pass into the deeper vessels; but their nocturnal distribution is of interest in relation to the fact that the intermediate host of this creature is the mosquito, whose habits also are nocturnal. The mosquito while drawing blood from the infected man itself becomes infected with the embryos of the filaria, which then undergo within its tissues the other phase of their life cycle. Thus it happens that on the death of the mosquito, if it should take place over water, which is its common habitat, or perhaps in some other way, the water becomes infected with that stage of the filaria which is capable of development within man. It is a curious roundabout sort of history, but it shows well what strange vicissitudes may be gone through by a parasite, and how circuitous may be the route taken by a disease germ, for such it is, in its course from one sufferer to another; and notwithstanding the warning we have already given against arguing from analogy, it is difficult, when discussing the life history of these various parasitic worms, to avoid the thought that in regard also to the much more minute micro-organisms which are the causes of those diseases spoken of as "infectious," some such alternate phase of life may be gone through, some intermediate stage between that in which the infection leaves the one patient and that in which it is received by the next. That this is so in some cases we know; that it may be so in many is a thing at least to be borne in mind.

Bilharzia Hæmatobia.

The Bilharzia hæmatobia is another parasite which is probably in many cases water-borne. Whether or no it enters into an inter-

mediate host has been questioned, some thinking that it passes one stage of its existence in some mollusc, along with which it is swallowed by people in the act of eating raw vegetables, while others believe that it obtains direct access to its victims while bathing in the water in which it is contained.

Distoma Hepaticum.

The eggs of the distoma hepaticum, or liver fluke, are also capable of development in water, and its embryos can swim, so that it is quite possible that it may be carried to man by water, as it pretty certainly is to sheep.

For a full account of these and other parasites see Vol. VIII.

Bacteria.

Preliminary Considerations.

Before entering upon a consideration of the diseases which are caused by those more minute organisms which are collectively spoken of as bacteria or microbes, it is necessary to discuss certain problems in bacteriology, and especially to insist on the wide distinction which exists between experiments in test-tubes and those in living animals, and on the very different results which are obtained according as bacteria are allowed to grow in a medium which has been proved to be well fitted for their development, or are placed in the tissues of a living animal and subjected to all the inhibitory influences which that animal is able to bring to bear upon them.

Again, before we can usefully consider the action of water in transporting these microbic disease germs we must recognize the great difference which exists between their growth in sterile water, in which they can develop without being interfered with by other organisms or their products, and their growth in ordinary flowing or stagnant water as it exists in nature, in which the, always more or less exotic, pathogenic organisms are exposed to the competition and perhaps to the actively destructive influence of native water microbes, organisms whose normal habitat is the water in which they are found and to which they have become exactly fitted and attuned by a long process of evolution. Still further again, we must consider how far the various types of water which are so often accused of acting as carriers of disease are of such a character as to be able to perform the rôle which is attributed to them.

Finally, it will be necessary to come to some conclusion on a very difficult question in regard to water-carriage of disease, viz., that of the influence of dosage upon the character of the resulting disease.

One of the most simple and elementary facts in bacteriology is that each microbe, whether a micrococcus, a spirillum, a bacterium, or a bacillus, when placed in fitting surroundings will multiply by repeated fission. What are fitting surroundings depends on the particular species, many kinds of bacteria being very susceptible to slight changes in the chemical nature of the medium on which they are placed, in its physical character as to moisture and the presence or absence of air, and in the temperature at which the experiment is made. It is in fact on the character of the surroundings in which they grow best, and on the influence which they exert on the medium in which they develop, that their identification to a large extent depends; their minuteness making it extremely difficult, if not impossible, to speak positively in this respect from their morphology alone. If, however, the right medium be used and the right temperature maintained, each microbe will undergo multiplication. On this is founded the well-known method of estimating the number of microbes by means of plate cultivations. By diffusing a measured amount of the fluid to be examined through a much larger quantity of gelatinized nutrient material, and then pouring this out on a plate and allowing it to set, a thin sheet of medium is obtained which is sterile throughout except at those points at which the now widely scattered microbes are embedded. It is possible then by counting the number of points at which growth takes place to estimate the number of originally existing microbes, it being assumed that, if the microbes are evenly diffused throughout the gelatin while this is in a liquid state, each "colony," each spot of growth, must represent at least one original micro-organism.

In the living body, however, matters are not so simple. We need not here enter into the question of the nature of the resistance offered by living tissues to the intrusion of microbic forms of life, but certain it is that bacteria for which living tissues form a perfectly fitting nutrient material, as shown by their growth and multiplication when they gain an entry in large numbers, are in some way destroyed and rendered harmless when they make their attack in smaller force.

The result, then, of an infection by pathogenic micro-organisms depends partly on the character and virulence of the microbes, partly, and even largely, on the resisting power of the individual attacked. Now the resisting power of the individual is an extremely variable quantity, and depends on many influences.

Many animals which are naturally immune to certain diseases become quite susceptible to infection by them when subjected to starvation, while others are equally deprived of their immunity by prolonged thirst. By exposure to fatigue also and loss of blood, ani-

mals which are naturally immune to certain diseases may be rendered susceptible to them, and the same effect may be produced by subjecting them to various other artificial and depressing conditions, such, for example, as exposure to heat, or cold, or to offensive exhalations, or submitting them to a diet which, although not deficient in nutritive material, is unsuitable to the digestive capacity of the animal in question.

It is extremely probable also that the particular phase of the digestive process during which an infection may be received, in those cases in which it enters by way of the digestive track, as of course is always the case in water-borne diseases, has a great deal to do with its power of obtaining a foothold in the body. When, roughly speaking, the digestion is in full activity, pathogenic organisms may be digested along with the other contents of the stomach and intestines, while at other times they may escape the action of the gastric and intestinal juices and may obtain a foothold in the intestinal mucous membrane. It must never be forgotten that the various microbes which are productive of disease in man, although often carried by water are by no means always at home in it, while other organisms in the same water find it exactly suited to their wants. It is not surprising, then, that in the water of many running streams, an infection with pathogenic forms may soon die out. The constantly acting influences which cause the less fit to be supplanted by the more fit, even though there may seem to be sufficient nutriment for both, lead to the destruction of the exotic pathogenic microbes in the presence of a crowd of ordinary water organisms.

Herein lies one of the difficulties in the way of attempts to purify an originally foul water. By mere mechanical filtration it is true that the great mass, perhaps the whole of the microbic elements may be removed, but so long as the chemical impurities remain in the water, in other words so long as the water remains charged with decomposable organic matter—matter the chemical affinities of whose elements are unsatisfied—so long will that water remain a fitting medium for the growth of microbes, and its character, so far as disease production is concerned, will depend on the sort of infection to which it may then be exposed. What is wanted is not so much a sterile water as one which is as far as possible incapable of supporting the life of pathogenic organisms. The experiments recently made in India by Mr. Hankin in regard to the efficacy of the permanganates in disinfecting wells which were known to contain cholera microbes point strongly to the importance of getting rid of the pabulum on which the microbes live as well as of removing the organisms themselves.

We now come to a very important question, which has been far too little considered by those who have dealt with the problem of water-borne disease, viz., that of the dose of infective material which is necessary to set up the disease in question. We may at once admit that this dose must vary very considerably, and that what is sufficient in some people to produce a definite attack is insufficient in others to cause the slightest obvious disturbance of health.

What, however, is the minimum dose required? Can it be admitted that a single microbe may set up cholera or typhoid fever? The importance of the question lies in this that it has been asserted again and again that the dilution of the poison, when a great river becomes polluted, say with typhoid excreta, is so enormous that it is impossible to conceive that it should remain effective as a cause of disease. The immediate answer to this would be that, as the poison is particulate, no amount of dilution could take away its efficacy, and that, although fewer people would be attacked, whoever did ultimately receive the germ might become infected by the malady. That would be the answer if we could believe that a single microbe could become actively pathogenic. But all bacteriological experience points the other way, and indicates the necessity of a considerable number of the infectious particles to produce the disease in those who swallow them.

There is no doubt that herein lies a difficulty.

The report of the Royal Commission on the London Water-Supply urges very strongly the mathematical improbability of typhoid fever being conveyed to the inhabitants of London by the water of the Thames, notwithstanding the fact of the presence of a certain number of patients suffering from that disease in the area from which the river water is derived.

The commissioners say that the total annual number of deaths from typhoid fever in those counties which practically form the water-basin of the Thames has varied during the years 1881–91 from 154 to 84, and that it is usually reckoned that for every death from typhoid fever there are from six to seven attacks; so that selecting for the purpose the year of highest mortality we may estimate the total number of attacks during that year, among the population of the Thames valley living above the intakes of the water companies at Molesey, as being 1,001. "Let us suppose, though such is of course an impossible supposition, that all the discharges of all these cases pass directly into the rivers, and let us see to what extent they would, in that case, undergo dilution; and in so doing let us assume the worst possible combination, namely, that the years of greatest

typhoid prevalence coincide with the years of smallest flow in the rivers. The smallest annual flow in the Thames over Teddington Weir, after adding the water previously abstracted by the companies, in any one of the eleven years 1881–91, was in 1890, when the total volume amounted to 294,792,000,000 gallons. The maximum estimated number of cases of typhoid fever in any one of these years in the Thames basin above Molesey was, as already stated, 1,001. This would give one case of typhoid to, in round numbers, 294,000,000 gallons of water, an amount which perhaps may be more readily apprehended if described as a mass five miles in length, one hundred yards in width, and six feet in depth. . . . In this calculation it has been assumed not only that the mortality was at its highest, and the river-flow at its lowest, but that all the discharges passed directly into the river. This latter assumption is, of course, ridiculous; the amount that can be supposed actually to pass in cannot possibly be more than an excessively minute fraction of the whole." After considering the time that the typhoid bacillus retains its vitality, the temperature necessary for its growth, and the great increase in the volume of the water in times of flood, they add: "Altogether we are led irresistibly to the conclusion, from the evidence put before us, that the amount of active specific typhoid poison that can get into the Thames or Lea, whether under ordinary conditions or in times of flood, is infinitesimally small when put into comparison with the enormous volume of water with which it will be diluted."

At first sight it might seem that this settles the question. An explanation of the difficulty, however, has been urged to the effect that although many microbes may be necessary to set up a disease in man, a very small number, a single microbe in fact, might be sufficient to infect a cistern, and that if such an event were to happen it would be easy to understand that a distinct relationship might be established between even a very sparse infection of the water and a series of apparently sporadic outbreaks of fever in the town to which it was distributed.

The Royal Commissioners, however, say: "We shall, we believe, be well within the mark in estimating the number of household cisterns in London to have averaged at least half a million during the past twenty years. Day by day water for drinking purposes has been drawn from each of these cisterns, and a fresh supply admitted from the mains, so that it is no exaggeration to say that there have been in the last twenty years thousands of millions of opportunities offered for the suggested catastrophe; and yet not a single instance can be adduced in which it has actually occurred." It should, however, be remembered that such an event would be almost impossible

of proof, which greatly detracts from the importance of any deductions which may be drawn from its apparent non-occurrence.

The probabilities are that the real explanation of the difficulty lies in the fact that the particulate infection, whether of typhoid fever or of cholera, is not evenly diffused throughout the water by which it is distributed.

Dr. Thorne Thorne, in a report on oyster culture in relation to disease, dated 1896, says: "Dealing, as we do, both in the case of enteric fever and of cholera, with an infection of a particulate character, we are concerned not with some material which is uniformly distributed throughout the whole body of the water to which it has gained access, after the manner of a chemical solution, but with microscopic bodies which may be widely separated, and which, though they may at one time tend to multiply and crowd together in microscopic masses, tend at another time to loss of vitality and to destruction. These are mingled with waters after the manner of a mechanical mixture, and occasional samples of water, whether selected or not, must often fail to exhibit them. Even when the contents of a certain well have been conclusively proved to serve as the vehicle of enteric fever, it has often been impossible to find Eberth's bacillus in many a gallon of the implicated water, whereas when a smaller quantity has been collected drop by drop throughout a continuous period of twenty-four or forty-eight hours, unmistakable evidence of the presence of this bacillus has more than once been forthcoming." This is a matter of considerable importance and will bear further consideration.

London is a town which is imagined to be supplied with well-filtered water, although the source from which the water is derived is acknowledged to be very foul. London also is a town which suffers but little from typhoid fever. Yet it is to be observed that the seasonal variation of the disease within the metropolis differs little from that in the surrounding districts.

If one looked upon typhoid fever as the result of a mere miasma, this need not give rise to any difficulty; but in view of the fact that water is well recognized as the ordinary means by which its infection is conveyed, the persistence of the same seasonal prevalence of the disease, both in town and country, is at the least curious, and is strongly suggestive of the idea that, notwithstanding all the filtering to which the water is subjected, the infective material is in some way carried from the country, whence the water comes to the townspeople who consume it.

Recent researches, undertaken by Mr. Shirley Murphy, medical officer of health to the London County Council, have raised this idea to something more than a suspicion; while the investigations of the

chemist to the County Council and others have tended much to explain the manner in which the infection has been distributed.

In the forty-ninth, fiftieth, and fifty-first weeks of 1894, the behavior of typhoid fever in the metropolis in regard to the number of cases notified was found to be exceptional, as compared with the previous four years. Usually during these three weeks a rapid fall in the prevalence takes place, so that by the end of the year the number of notifications has fallen to below the average for the year. But in 1894 the notifications rose instead of falling during this period. On inquiring into the cause of this peculiarity, it was found that notable floods occurred at the time, antecedent to the abnormal prevalence of enteric fever, at which some new factor in the dissemination of the disease in London might be expected to have come into operation if the infection were water-borne.

The importance of this matter of floods arises from the fact that the filtration to which London water is subjected, although it removes a very large percentage of the microbes, rarely removes them altogether, so that when the water in the river is fouled by floods the water in the pipes is proportionately less pure in a microbial sense. The inquiry was carried further, and it was found that certain districts supplied by the water companies outside the London district showed the same abnormal rise in the number of notified fever cases in these weeks, while in other districts not supplied from the river this rise in fever prevalence did not take place. One of the water companies in London, however, draws its supply of water from a deep well, and in the district supplied by this company the abnormal prevalence of typhoid fever in the weeks in question did not take place. There was then a known and exceptional fouling of the water at a certain date, followed in due course by an exceptional prevalence of typhoid fever in those districts, both within and without the metropolitan area, which were supplied with river water, while in certain other districts, not so supplied, the prevalence of fever took its normal course.

Summing up the matter, Mr. Shirley Murphy, who from his official position naturally spoke guardedly, was of opinion that the hypothesis of a water-borne contagium was the one which was best able to explain the increase of the disease in the weeks in question. The epidemics of typhoid fever in the Tees valley, to be mentioned later, furnish another instance of the infection of typhoid fever retaining its activity when mixed with such a mass of water as to be almost infinitely diluted. As has already been stated, the explanation lies in the fact that the particulate infection is not equally diffused throughout the whole mass of the water.

This has since been shown with great positiveness to be true in regard to the London water by Mr. Dibdin, chemist to the London County Council, and other inquirers associated with him, who have not been content to examine small samples of water but have collected the residue left after the filtration of very considerable quantities, and have thus been able to show not only that a large number of microbes pass the filter beds, as of course was known, but that at times the filtration is so managed that much larger creatures than bacteria can get through.

In regard to this important question as to the quantity of pathogenic material necessary to set up a disease, it must be answered that but for the vital resistance of the living tissues of the body to the intrusion of other forms of life, there is no reason why a single pathogenic microbe should not give rise to the malady associated with it. In such a disease then as cholera, in which the main growth of the associated micro-organism takes place in the intestinal canal, that is, not within the substance of the living tissues, an infinitely small dose, possibly even a single microbe, might in certain conditions of the intestinal contents so multiply among them as to produce such a quantity of toxic products as to set up the symptoms of the disease.

Where, however, the growth of the microbe within the tissues of the larger organism is essential to the development of the disease, it is not easy to reconcile the possibility of such minimal dosage with what we know about the power possessed by healthy bodies of resisting the intrusion of microbic life. The probabilites—and in this matter it is impossible to do more than speak of probabilities—are that for the production of such a disease as typhoid fever a comparatively substantial dose, one much larger than any single microbe, must be taken before symptoms can be produced, and in fact it will be found that in a large proportion of the cases in which typhoid fever has been shown to be water-borne the water has been subjected to a pollution of a comparatively gross character, and that however much the infective particles may have been scattered by dilution, there has been a fair opportunity for these particles to be individually of such a size as to contain quite a colony of micro-organisms, sufficient, if one may so say, to take care of themselves. In many instances there has been proof of an actual communication between a closet and a well, or between a drain and a water pipe, or there has been a history of the entry of infected surface washings into a water supply which has after that been but imperfectly filtered even if filtered at all. In all such cases it is quite unnecessary to introduce the question of single microbes, seeing that in all of them there are opportunities for the infection being carried by particles of much larger size. But

even in regard to infection by public, and presumably filtered water supplies, the same holds true, for well filtered as they may be at times, there is too much reason to believe that at other times water which is practically unfiltered is allowed to pass. This has certainly been the case in regard to the Thames water supplied to London, which, however good its usual character, has been shown not infrequently to contain impurities of such a nature as to prove the occasional inefficiency of the filtering process to which it has been subjected. Even then in regard to typhoid fever distributed by public water supplies, we are not driven to the hypothesis of the disease being originated by a single microbe, seeing that, according to the various reports presented to the London County Council, the London water not infrequently contains far grosser impurities.

It will be well, however, before entering on the discussion of the purely clinical side of the question, to insist again on the fact that we as yet possess very little accurate knowledge as to the intimate mechanism of the processes by which any of the infectious diseases are carried from one individual to another. In the bulk, and by ordinary methods of clinical and statistical observation, we are able to assure ourselves that certain maladies are capable of being transmitted from man to man, and we are at times so far able to trace the route by which the infection travels as to be able to assert that they are water-borne. Far beyond this, however, we cannot at present go. Even in regard to the most infectious of diseases, viz., small-pox, we may show by statistics that the contagium, whatever it may be, can travel long distances through the air; but when we come to details, it is indeed difficult to form any satisfactory and convincing mental conception of the nature of the process by which this infective material is given off during the early acute stage of the disease, or of the manner in which it is absorbed. This, however, may be said: that while small-pox, measles, and scarlet fever are diseases the most marked lesions of which appear on the skin, it is as certain as such things can be that it is not by the skin that the infection is absorbed. So also we must take care not to assume too readily in cases of typhoid fever, and even in cases of cholera, that because the chief manifestation of the disease centres in the intestinal tract, therefore the infection must have been there deposited and there absorbed. Certainly in regard to cholera a pretty strong inference may be drawn to that effect, but as to typhoid there seems no proof whatever as to the point of entry into the tissues. We know that the micro-organism goes in at the mouth, but we know nothing as to what happens afterward or by what route it arrives at the parts where it ultimately develops.

The only answer which bacteriology can give to the question how

far zymotic diseases are water-borne, is the statement that the microbes on which certain of them, such as cholera, typhoid fever, and some others depend, are capable of being carried from man to man by means of water. How far they actually are so carried has to be decided by other lines of investigation, which will be mentioned under the heads of the different diseases.

Typhoid Fever.

Typhoid fever may be taken as a type of a water-borne, zymotic disease and will therefore be dealt with in considerable detail; but it may be broadly stated that much that is true of typhoid fever, in regard especially to the mechanism of its distribution by rivers, wells, conduits, water pipes, etc., is true also in regard to cholera. In fact it is not too much to say that any place the sanitary arrangements of which are such as to lead to a prevalence of typhoid fever is exposed to danger of epidemic cholera, should that disease once be introduced.

It is now generally recognized that typhoid fever is a specific disease caused by the body being infected by a bacillus which is usually to be discovered during life in the stools and urine, and rarely in the blood, and after death in the various tissues of the body, especially in the intestines, in Peyer's patches, the mesenteric glands, the spleen, the liver, and the kidneys.

It has a febrile period of about three weeks, and during a considerable part of this time the infection is being discharged in the stools and in the urine. Diarrhœa also is common in its course, so that the amount of infective material which is discharged from a single case is often very considerable.

Typhoid bacilli, however, are rarely to be found in the stools before the ninth day of the disease, and they may disappear before the fever ceases. Probably their persistence depends to some extent upon the extent to which ulceration has taken place in the intestines, for in some cases they have been found to be present in the stools many days after the cessation of the fever.

In the urine the bacilli are said to have been discovered as early as the third day. According to Horton Smith, however, this is not so; true typhoid bacilli, as identified by the most recent tests, not appearing in the urine until the third week. They have also been found in the sputum of patients in whom typhoid fever was complicated with pneumonia.

The knowledge that infective particles are discharged in the course of the disease among the excreta of the patient makes it necessary to inquire as to the modes by which this infection may be conveyed again to man.

Typhoid fever, like other infectious diseases, attracts most attention when it occurs in epidemic form; but it very commonly occurs as a sporadic disease, and no account of its mode of spread can be considered complete or trustworthy which does not take cognizance of the sporadic as well as of the epidemic outbreaks.

As regards its actual mode of entry, then, it may be said that it may be by way of air, food, or drink, especially the latter.

When a patient becomes infected by way of air, it is probably in most cases from inhaling dust containing typhoid bacilli. In hot weather when clouds of dust arise from land which has been manured with human excrement, where, for example, the dry earth system has been carelessly carried out, it is clear that many risks must be run by those who inhale such dust if, as must often happen, it contains fragments of the dried excreta of typhoid patients. Mere drain air, however much the sewage itself may be infected, is probably not a direct carrier of infection. That it has an influence, however, on the prevalence of the disease seems almost certain. Probably it may be the case, as already stated, that the respiration of foul air, although not specifically infected, has a predisposing influence which leaves those who breathe it especially liable to infection. The observations of Alessi point strongly in this direction, for he found experimentally that animals exposed to sewer gas fell victims to specific infections which were not fatal to others living out of its reach. In his experiments he found that rats, guinea-pigs, and rabbits, when exposed to emanations from a cesspool, gradually increased their susceptibility to infection by the typhoid bacillus. "After an exposure of from five to seventy-two days in the case of rats, seven to fifty-eight days in the case of guinea-pigs, and three to eighteen days in the case of rabbits, the resistance of the animals was so diminished that inoculation with relatively small amounts of cultures of the typhoid bacillus proved fatal in from twelve to thirty-six hours" (Abbott). The bacilli were found in the blood, liver, and spleen.

In regard to infection by food, the modes in which it may happen are various. Air-borne dust is even more likely to cause disease by way of the food on which it settles than by being directly breathed, and in places where the kitchens and larders are arranged in close proximity to latrines or earth closets, it may not infrequently happen that food may be seriously polluted in this way.

Equally may the infection not only of typhoid fever but of cholera be carried to food by flies. During late years the possibility of this has been abundantly demonstrated, and in regard to cholera the transference of the bacilli to milk by the agency of flies has been shown to have taken place. It undoubtedly may happen that the

bacilli may develop within the fly and that thus the infection may be deposited in food or water on the death of the fly; but by far the most common manner in which flies carry infection is by means of the dirt which adheres to their feet and bodies. It has been noticed again and again in India that when the excreta of cholera patients have been carried out of the hospitals the bearers have been surrounded by swarms of flies which have afterwards dispersed to settle on other objects, and in this way it has been found that bowls of milk past which these excreta were carried quickly became infected with cholera bacilli. The extent to which flies are able in this way to carry bacilli about with them was recently demonstrated before the Royal Society by Mr. W. T. Burgess. Flies had been placed for a moment in contact with a cultivation of bacillus prodigiosus and then allowed to escape into a large room. After a varying number of hours they were recaptured and made to walk for a few seconds over slices of sterilized potatoes which were then incubated for a few days. The experiments showed in an unmistakable manner that the fly tracks on the potatoes were marked by vigorous growths of the chromogenic organism, even after several hours had been spent by the flies in active exercise since their exposure to the source of infection. The bearing of these experiments is obvious, not only in regard to the infection of food, but as indicating a manner in which water may become infected when it is preserved in open jars or cisterns.

Not only may food become infected after its preparation in the ways already mentioned, but fruits and vegetables not uncommonly run risks of the same accident during their preparation, by being washed in specifically polluted water, or during their growth by being manured with specifically polluted excreta. A good deal has recently been heard of infection being distributed by means of oysters, and many very careful researches have been made as to the manner in which and the extent to which it takes place. But although oysters must be looked upon as a food, the distribution of typhoid fever by their means is really but another example of the spread of the disease by aid of water.

A very careful report has recently been issued on this subject by Dr. Thorne Thorne, medical officer to the Local Government Board, dealing not only with the English cases but with some that have appeared in other countries, among which the following history, given by Dr. Chantemesse in a paper on "Oysters and Typhoid Fever," in a communication to the Académie de Médecine in Paris, appears worthy of record: After the complete absence from the little town of Saint André de Sangoins, in the Mediterranean department of Herault, of typhoid or enteric fever for about a year, a barrel of oysters

was received in the town on February 15th, the contents being eaten raw by fourteen persons living in six houses. These oysters came from Cette, a port on the coast of the same department; and, according to the commission subsequently appointed, the oysters in question had been stored in waters highly contaminated with sewage. All the fourteen persons who partook of the oysters were taken ill, whereas other members of the same households, including servants who had taken no oysters, remained well. Of the fourteen persons attacked, eight suffered from such symptoms as abdominal pain, vomiting, loss of appetite, and general malaise. Four others who were young and who had only sparingly eaten of the oysters were attacked with symptoms of greater severity and lasting from a fortnight to twenty-five days; these symptoms including dysenteric diarrhœa, swelled abdomen (painful on pressure), great prostration, and bowel discharges described as infective. The remaining two persons, aged twenty-one and twenty years respectively, suffered from exceptionally severe attacks of enteric fever, one case terminating fatally.

This occurrence was, in Dr. Chantemesse's opinion, so characteristic of attacks held to have been related to the consumption of molluscs that he set himself to ascertain how far there was evidence that oysters purchased from the principal merchants of Paris, and professedly derived from different layings and countries, could be regarded as capable of bringing about similar results. The oysters collected for this purpose, which appeared to be in every respect in excellent condition, were submitted to bacteriological examination; and among the numerous micro-organisms which they exhibited, colon bacilli were found in goodly number. Some of these oysters were then placed in sea water which had been intentionally contaminated with typhoid discharges and with the typhoid bacillus; and after remaining under these circumstances for twenty-four hours, they were taken out and kept for a further period of the same duration, this being held fairly to represent the period commonly elapsing between their removal from the oyster layings or ponds and their consumption as food. The oysters, which were alive and quite normal in appearance, were then submitted to bacteriological examination, with the result that living colon bacilli and also typhoid bacilli could be recovered both from the "liquor" and from the bodies of the oysters.

The danger evidently chiefly arises from the fattening beds and the storage ponds, from which the oysters are taken for despatch to market, being placed in unsuitable situations. For purposes of convenience, both in regard to accessibility and facility for procuring labor at reasonable cost, the cultivation of oysters is carried on at

points on the coast which are near to towns and villages, while for "fattening" the oysters during the later stages of their development preference is given to river estuaries or their neighborhood. There is thus a tendency to use for purposes of oyster cultivation localities which are apt to be more or less polluted with sewage, and there seem ample grounds for the belief that the risk of dangerous specific infection of oysters is much more pressing as regards such layings as are used as fattening beds, and such pits as are used for storage purposes, than as regards other layings from which oysters are not despatched directly to market. The description given of these fattening beds shows how greatly exposed some of them are to sewage contamination. "It seems almost beyond comprehension," says Dr. Thorne Thorne, "how any one could venture to 'fatten' oysters for human consumption in a river such as this (the Medina in the Isle of Wight), which is fouled above the layings by the crude sewage at Newport, with its 10,000 inhabitants, by the effluent from the neighboring prisons and barracks, and by the overflow from the workhouse cesspool; and which receives into it, immediately below the layings, the contents of eight other sewer and drain outfalls from East Cowes and West Cowes."

At Southend, again, "where there are two layings, it was found that at one to the west of the pier the oysters are placed between two principal sewer outfalls, to say nothing of the proximity of minor outfalls, at a point where the sea bottom and the matters floating on the surface afford the most obvious proof that the conditions are filthy in the extreme."

There seems then no possible doubt that oysters have many opportunities of becoming polluted by sewage, and in regard to the question whether the typhoid or the cholera microbe with which such sewage may perchance be infected can so far retain its vitality as to be capable of gaining access to the oyster along with the sewage, it can only be said, as has already been stated when treating of the viability of these bacilli, that such an event is certainly possible.

Although Dr. Klein, who conducted this part of the investigation for the Local Government Board, was able in only one instance to discover Eberth's typhoid bacillus in the body and liquid of oysters as supplied to the trade, he abundantly proved that when oysters had been placed in sea-water to which typhoid bacilli had been added, the bacilli could be recovered from within their shells as late as the seventeenth day, no fresh bacilli having been added in the mean time. The investigations on the same subject recently undertaken by Dr. Cartwright Wood on behalf of *The British Medical Journal* emphasize the same point even more forcibly, so that there need be no hesitation

in accepting the possibility of the conveyance of the infection of typhoid fever by oysters; and that such infection is so carried has now been shown in a large number of cases. Of these perhaps the most interesting and convincing is the case of an outbreak of typhoid fever at Wesleyan University, Middletown, Conn., related by Dr. H. W. Conn in the Seventeenth Annual Report of the State Board of Health of the State of Connecticut.

The college has both male and female students, but the typhoid fever was limited to the males. A careful consideration of all the surroundings both in regard to the college buildings, the homes of the students, and the ordinary articles of diet appeared to exclude all the more ordinary vehicles of infection such as water, milk, and sanitary defects in the plumbing.

It was an important point, however, that between October 20th and November 1st over 20 cases had occurred, but that after that date they declined in frequency, although one case occurred so late as November 9th, all of which pointed to the source of infection having been in activity for only a short time. It was then ascertained that all the cases of typhoid, with three exceptions, occurred among members of three college fraternities or clubs, of which there were seven in the whole college, all the members consisting of male students. These three fraternities contained among them 100 students among whom 25 of the 28 or 29 cases of typhoid had developed. It was evident that whatever the cause it had some relation to the doings of these fraternities, but it was found that the clubhouses were in different parts of the town and connected with at least two different sewers. It was, however, found that on October 10th, eight days before the first case, an initiation supper had been given by each of the fraternities, and on inquiring into the food eaten it was found that each of the three fraternities involved had been supplied by the same oyster dealer with oysters which were eaten raw; while at the other four fraternities two had had no oysters, a third had cooked oysters, and the fourth had oysters from an entirely different source. Moreover, of the three students who were attacked with fever, although not connected with the fraternities, one had been a guest at one of the suppers and another had eaten raw oysters in the store of the oyster dealer. Then there were a considerable number of guests from other places, and it was found on inquiry that among these several cases of illness had occurred, four of which were clear cases of typhoid fever which took place about the same time as those in the college. On investigating the source from which the incriminated oysters had been supplied, it was found that, although they had grown in the deep water of Long Island Sound, they had been deposited in the mouth

of a fresh-water stream for a day or two to fatten, and it was further ascertained that within about a hundred yards of this place was the outlet of a private sewer coming from a house where a lady and her daughter lived who were at that time in the early stage of typhoid fever, they having just come under medical treatment on October 11th for an illness which turned out to be typhoid fever.

It was also found that several cases of typhoid fever had occurred at Amherst College among members of a fraternity who, at a fraternity supper held on October 12th, had eaten raw oysters which had been fattened at the mouth of the same creek; and a young man from Boston who suffered from typhoid fever simultaneously with the rest was found to have visited Middletown about the date of the banquet, and while there to have eaten raw oysters, in fact, to have partaken of the one lot which had been sold by the Middletown dealer to be eaten raw.

Dr. Conn summarizes the matter thus:

"1. The dates of the cases appearing at Wesleyan, all between October 20th and November 9th, plainly point to a single source of infection to which all the afflicted students were exposed at about the same time. This must have occurred a little more than a week earlier than the appearance of the first case, and the initiation suppers perfectly fill the conditions.

"2. That these initiation suppers were the source of infection is rendered certain from the fact that four of the visitors who attended these banquets and have had no further connection with the fraternities, have developed typhoid simultaneously with the cases in college, and by the further fact that two visiting Yale students who attended the suppers have similarly suffered from typhoid.

"3. The fact that only three out of seven fraternities holding suppers on that evening suffered from typhoid, pointed to some article of food or drink used at these three suppers and not used in the other fraternities.

"4. The fact that about twenty-five per cent. of the students attending the suppers have suffered from typhoid pointed to a universal and very active source of infection, and not to an incidental one. Whatever article of food contained the infectious material must have been eaten by nearly every one present to account for such a large percentage of cases.

"5. Only one article of food or drink was used by the three societies which was not used equally by the other four fraternities. This article of food was oysters, and they were eaten raw.

"6. These oysters came from a creek, where they had been allowed to fatten for a day or more within three hundred feet of the outlet of

a private sewer, and in such a position as to make contamination from the sewer a possibility. At the time that the oysters were there deposited there were two persons in the house supplying the sewer who were in the incubation period of typhoid fever, a period during which no attention would be paid to their excreta.

"7. Typhoid germs are not injured by sea-water or oyster juices, and if they found their way into the oyster would certainly have lived long enough to be sent to Middletown and be served in the tables of the fraternities.

"8. Twenty-three cases of typhoid fever followed among the students in attendance on the suppers at which the oysters were eaten, and six among persons in attendance and not among the present students at Wesleyan. In all of the cases of undoubted typhoid it has been possible to trace either direct or indirect connection with these oysters. The oysters were also eaten raw by one family in town, and at least one severe case of typhoid followed.

"9. The use of oysters from the same locality by the students at Amherst College produced, or at all events was followed by, an outbreak of typhoid fever among the students who eat of them. These facts, taken together, form a chain of evidence practically complete at every point and leaving no room for doubt. Whatever may be said in regard to oysters in general the Wesleyan outbreak of typhoid was caused by a special lot of contaminated oysters."

It would seem probable that in many cases the *modus operandi* of infection by oysters is that when the oyster is deposited, either for fattening or storage, in some handy and convenient place situated within the area contaminated by a sewage outfall, some more or less gross particles of excrementitious matter are taken into the cavity of the shell and become lodged in the folds of the creature within, and that these particles are swallowed bodily by whoever eats the oyster in question.

The sanitary conditions of the locality where the oysters develop is perhaps of small moment, but that of the last place in which they open their shells and allow the water to enter freely is of the greatest importance, for on it depends the character of the fluid the oysters take away with them.

In regard to the presumed rarity of infection by oysters in comparison with the enormous number eaten, it is necessary to bear in mind the series of coincidences which must occur to make such infection possible; and this applies to all other shell-fish eaten in the same way. Dr. Thorne Thorne says:

"When the oyster trade of Great Grimsby came under suspicion in connection with the cholera prevalence of 1893, it was stated that

if there were any truth in the alleged risk the resulting mischief would have been on a far wider scale than was actually the case. I ventured, at that time, to point out that in order to enable a given sample of oysters to convey the infection of any specific disease, such as those which are here in question, it would be necessary that the shell cavity or body of the mollusc should retain some portion of the sewage—often in a state of great dilution—to which it had been exposed; that such portion of sewage should actually contain the specific infection; that this specific infection should not be destroyed by antecedent cooking or otherwise; and that the oyster or oysters should be consumed by some susceptible person. And I indicated that the coexistence at one and the same time of all these conditions was not likely to be of frequent occurrence."

It should be borne in mind in regard to this, as in regard to many other matters, that although sanitarians are glad enough to find their conclusions supported by the investigations of bacteriologists, it is not on bacteriological theories and details of laboratory work that sanitary science mainly depends for proof of the modes by which infection is distributed. In the case of the oyster, "enteric fever has been ascertained to have followed on the consumption of raw oysters; the interval between such consumption and the onset of the symptoms has corresponded with the incubation period of the disease; the special incidence of the disease has been on those who were known to have partaken of the oysters, while others, who would only be differentiated from the sufferers in that they had not partaken of the oysters, escaped. The consumption of oysters has been ascertained by a process of exclusion to have been the only medium through which such a disease could have been simultaneously communicated to the sufferers; and at times the oysters in question have been found to have had opportunity of contamination by human excreta, even by specifically infected excreta." Such evidence is enough, even without the microbe. But when we find on tracing the life history of the micro-organism which has been shown by other means to be causally connected with the disease in question, and which is known to be poured with sufficient profusion into the sewers, that it can live therein, that it can live in sea-water, and that when it gains an entry within the shell of the oyster it can live there also for quite time enough to enable the oyster to be brought both to market and to table, the ordinary common-sense proof which is sufficient in itself receives strong confirmation; and it is unnecessary to point out how greatly each line of proof is strengthened by its agreement with the other.

It is by drink, however, far more than by either air or food, that

the infection of typhoid fever is carried from man to man. Even where infection is attributed to food it is very commonly the case that water is the actual agent involved in the transference of the microbe, and that if proper care had been taken in regard to the water employed in culinary and other processes the food would never have developed its infective properties. Hence the phenomena of water-borne typhoid became the key by which the distribution of the disease even by other agencies is often to be explained.

One of the most important points to be borne in mind in regard to the etiology of this disease is that many of the cases are of such slight severity that they are able to go about during a considerable part, perhaps during the whole of the progress of the malady. Thus it happens that the infection is carried into fresh places and over long distances by persons who are not known to be ill, and who recover without leaving any trace of their having been agents in its dissemination. Travellers, vagrants, and honest wanderers in search of work, from the irregularity of their lives in regard to food and drink, are much more liable than others to become infected, and in fact often break down from typhoid fever in the course of their wanderings. So long, however, as they are able to keep on the move the habits of the vagrant class render them peculiarly liable to spread the disease among the inhabitants of the districts through which they pass; and, although it is true that civilized communities ought to do much more than they are apt to do to secure pure water for domestic and dietetic use, it is also true that this is not altogether a matter of water works and engineering, but that one of the steps necessary for this purpose is the regulation and suppression, so far as may be, of the nomadic parasites of civilization, the vagrants who acknowledge no responsibility, contribute to no rates, and submit themselves to no rules as to decency of behavior. These people revert to natural methods in regard to the disposal of their excreta, and there can be little doubt that many of those untraceable and apparently mysterious outbreaks of typhoid fever which have led some investigators to imagine that the disease must originate *de novo* have really been caused by the pollution of rural watercourses with typhoid excreta deposited by infected vagrants wandering across the country.

It would, however, be incorrect to suggest that the etiology of typhoid fever is so simple an affair as to be expressed by the crude assertion that infection is necessarily the direct outcome of the ingestion of water directly polluted with typhoid excreta. It is well known that such a pollution will produce it, and numerous examples will be given later on to prove this point; but in many cases, especially where the disease appears to be endemic, the relation is much more complex.

There is every reason to believe that the microbe of typhoid fever plays a double rôle, and that, although it is best known as a parasite, it also exists as a saprophytic organism, able to maintain its life for long periods quite independently of man. It has even been maintained that some such alternation of its phases of existence is necessary to the development of its infective power, and this hypothesis receives some support from the opinion held by many that fresh typhoid stools are not infectious, and that it is only after a certain period has elapsed, or, in other words, after the bacilli have had an opportunity of multiplying outside the body, that their infective properties attain their full virulence. In any case, however, when the typhoid bacillus gains access to the body, and becomes implanted in human tissues, it again takes on its parasitic life, and sets up that definite train of symptoms—some the result of the absorption of toxic products formed in the course of its growth, others the outcome of the active resistance of the tissues—the sum-total of which go by the name of typhoid fever.

While, then, in many cases it will be found that typhoid fever can be traced back to a direct infection, the patients having taken water which could be proved to be polluted with typhoid excreta, in many others the infective organism must have lived a saprophytic life for some time, must indeed have passed through many generations of growth between being excreted by one patient and absorbed by another. Herein, it may be observed, lies one great difference between epidemic and sporadic outbreaks of the disease. A water supply, whether a spring or well, a running brook, or a reservoir owned by a company or municipality, is usually shared in common by many people, and a direct infection of such a source is almost of necessity followed by a widespread distribution of the germs of the disease. The extent and the incidence of the resulting outbreak will no doubt be largely influenced by the susceptibility of those who drink the water; but at any rate their opportunity for developing the disease will be widely spread, and as a fact it is commonly found that the direct infection of a water supply is followed by an outburst which is sudden in its developments, is widely spread within the area in which the infected water is distributed, and is at first limited to that area.

These are the ordinary characteristics of what is spoken of as "water typhoid" or "milk typhoid," which is only another form of the same thing, it being the water in the milk or the water used in the treatment of the milk cans which is the cause of the mischief. It must, however, be remembered that typical as are some of the reported instances of water typhoid, especially where, but for the

infection of the water, the sanitary conditions of the place are good, it is no uncommon thing to find that although the early days of an outbreak show the characteristic type of a water epidemic, this soon fades off into a widespread prevalence, the relation of which to any water supply can no longer be traced with any accuracy. The fact is that, given the occurrence of an epidemic of typhoid in a place in which the sanitation is bad, whatever may have been the cause of the original outbreak it continues, and it spreads in response to influences which may or may not have to do with water, but have at any rate nothing to do with the original water infection which started the epidemic.

This is a matter which it is of some importance to recognize, for it applies fully as much to cholera as it does to typhoid. Here lies the great difference between the final results arising from the introduction of an infection into a district, according as its sanitary appliances are good or bad. In the one case, so soon as the cause of the outbreak is discovered and the use of the polluted water is stopped, the epidemic ceases; in the other, the typhoid bacillus gains a foothold in the place itself, and, although it may not become permanently endemic, a prevalence of the endemic type persists for a considerable time, long after the original defect has been rectified.

It is extremely difficult to follow the ins and outs of the typhoid infection when sporadic cases keep cropping up at considerable intervals of time, and when there is no apparent connection of the cases with each other beyond the fact that certain villages and certain houses appear more prone than others to the disease; and it seems not unfair to suppose that in such cases the soil, and perhaps even the houses themselves, may have become infected with the bacilli, may, in fact, be affording them a nidus in which they may develop and keep up their vitality until the time arrives when, as the result of some sanitary sin, some dirty trick, some lack of care in maintaining the cleanliness of food or water, the poison again finds access to a susceptible individual, and the disease again appears, to be once more carried about by the patient, and again to set up fresh outbreaks wherever he may deposit his excreta.

In many of these cases in which typhoid fever occurs sporadically and quite independently of any widespread water epidemic, the disease still is water-borne so far as the final act of carrying the infection to the mouth is concerned.

In regard to the apparent anomaly involved in the water carriage of sporadic cases occurring at long intervals, it is necessary to bear in mind the small proportion of those exposed to the chances of infection who suffer from the disease, even where, as when the water

supplies of large towns are affected, the pathogenic organism is known to have been swallowed by a large number of people. A very simple calculation on this basis is sufficient to show that, even where the bacillus has taken root in the soil so that the cause of the disease is practically endemic in the locality, the disease may be a long time in appearing, and when it appears may affect only a small number of people and then only at considerable intervals of time. Where a cesspool or a drain leaks directly into a well, the conditions exist for the development of an active and virulent outbreak affecting a considerable number of those who use the water from the well in question. The dose of infection in such cases is probably much larger than is usually the case in any outbreak arising from the implication of public water supplies. Nevertheless, even in such cases a considerable number of the drinkers escape. But the infection of a local water supply, a farm well, for example, by soil-grown typhoid, is a very different thing from its infection by a direct leak from a typhoid-poisoned cesspool; the infection of the well may be only intermittent, the dose is less, and the proportion of drinkers whom that dose is able to affect is smaller. Although the microbe may be almost permanently present, growing as a saprophyte in the soil, it may only at long intervals obtain a foothold in the human body, partly from the rarity with which it meets with a susceptible individual among the small number of people who partake of the infected water, partly from the fact that it may only be during exceptional conditions of rainfall that the bacillus, although existing in the soil, may take on active growth or gain access to the well or other source from which drinking-water is drawn.

This point is one of no small interest. It has been too hastily assumed by some that the only rôle played by excessive rainfall is as a carrier of filth which has been accumulated on the surface of the land into the watercourses which drain it. Typhoid excreta have been looked upon as so much poison lying dead and inert until washed into the watercourses, carried back again to man, and so brought again into activity as producers of disease. This, however, is but a very imperfect conception of what goes on in typhoid-sodden soils. In them it is not a mere question of washing accumulations of filth off the surface, but of draining out of the soil itself organisms which have grown in it—the descendants doubtless of microbes which have been implanted in it by previous contamination by typhoid excreta, but themselves quite innocent of any direct connection with any recent case of typhoid fever. It is in regard to this aspect of the case that Pettenkofer's "ground-water theory" is of so much interest. He showed that, in Munich at any rate, there was a connection be-

tween the movements of the ground water and the prevalence of typhoid fever. This was not a matter of level but of alteration of level. His observations were to the effect that the number of the cases and of the deaths from typhoid fever fell with the rise of the subsoil water, and rose with the fall of it, the prevalence of the disease being in proportion not to the level attained at the moment by the subsoil water, but only to the variation of level which was then taking place. These observations, so far as regards certain places, have been confirmed by subsequent observers, while in regard to others they have been refuted; so that, although Pettenkofer's observations were right in regard to the localities dealt with, it cannot be said that the ground-water theory is correct as a general or universal law. In fact it is quite clear, as will be seen by the cases which are given later on in this article, that in very many instances the occurrence of typhoid can be definitely traced to a localized fouling of the water supply taking place at a considerable distance from the place where the outbreak has occurred, and that no condition of the ground water at the latter place can have had anything to do with the outbreaks in question. These, however, are cases of infection of public water supplies, reservoirs, conduits, etc., and are in quite a different category from those in which an occasional or a periodical epidemicity has been grafted on to a more or less endemic prevalence of the disease. In such cases, with our knowledge of the microbic origin of typhoid fever and of the power possessed by the microorganism associated with it of leading a saprophytic existence, it is easy to see how important a part may in some places be played by oscillation of the level of the ground water in causing a multiplication of the infective organisms and perhaps in increasing their virulence.

Laboratory experiments show that certain conditions as to heat, moisture, access of air, and character of nutrient medium are necessary for the production of the best results in the cultivation of microorganisms, and there is reason to believe that little influence as the movements of the ground water may have in producing outbreaks of typhoid where the water supply comes from pure sources at a distance, they may have a great effect in producing those conditions which are most appropriate for the growth of the bacillus in a sewage-sodden soil, and may thus lead to a prevalence of fever among those whose water supply is gathered from it, or whose dwellings are so situated and so contrived as to draw air from the infected subsoil. We know far too little about the mode in which foulness of the ground air affects the health, but it is worth while to observe that variation in the level of the ground water involves variation also of the amount of the ground air. It is to be noted also that while the

ground water is rising, the damp layer, the layer in which microbic life can be carried on with greatest vigor, is being continually submerged as the water advances upwards, while when the ground water sinks it leaves behind it an ever-increasing thickness of moist soil aerated by the air which is drawn in after the retreating waters, and polluted by the soakage from the surface which took place during the preceding rains.

In regard to this the following passage from Notte and Firth's "Hygiene" is worth quoting: "Criticising these views of Pettenkofer's, Ranke has pointed out that no enteric fever exists in the neighborhood of Munich but what is imported from Munich itself, although both the soil and ground water are the same. Munich has a soil consisting of fine sand, with a peculiar power of holding nitrogenous substances; it is largely honeycombed with cesspools, from which more than ninety per cent. of the contents soak into the surrounding soil, and, as the streets are well paved, the houses of the town constitute the only outlets for the foul soil air. A very similar argument, together with some very interesting facts concerning the prevalence in Dublin of enteric fever, have been brought forward by Sir C. A. Cameron. For some years a persistent occurrence of this disease has existed in Dublin, which cannot be accounted for either by polluted water, milk, or food, and which has not very sensibly decreased even after an improvement in the water supply. Sir C. A. Cameron attributes this prevalence to the practice, which has been in use in Dublin for years, of storing excreta in pits, so that the soil has become thoroughly saturated with the specific organism of the disease; these he thinks are carried into the atmosphere by displacements of ground air. According to him, the ratio of cases to population living in Dublin, on a loose, porous gravel soil for the ten years 1881–91, was 1 in 94; while the ratio for those living on a stiff clay was but 1 in 145. 'This is what we should expect, since the movements of the ground air are much greater in loose, porous than in stiff clay soils.'"

The question of air-borne typhoid is beyond the scope of the present article, but it is worth while pointing to the fact that any conditions which could produce an infective ground air would certainly produce an infective ground water, and however completely a town may appear to be furnished with a piped supply of municipal water, there is no safety so long as the pipes are surrounded with an infected subsoil. There are two ways in which even high-pressure water pipes may become fouled by absorption from the ground in which they are laid. On the one hand, whenever the water is turned off for repairs, and especially, as in the case in many otherwise fairly

sanitary towns, London for example, where the supply is intermittent and is turned off for a considerable portion of every day, every leak in every pipe draws in water from the subsoil—pure water if that is pure, but foul if the subsoil is foul, as it usually is in towns.

This in-sucking of foul subsoil water is by no means so uncommon an occurrence as people might imagine. A very large quantity of water is constantly lost by the water companies in consequence of the leakiness of their pipes, and wherever there is a leak when the pipe is full there tends to be an in-sucking when the pipe is empty. In gravel soils especially leakages are common, because the effused water runs away, and thus the leak is not so quickly discovered as otherwise might be the case; and cases have occurred in which the safety of the road above has been seriously imperilled by the gradual washing away of the soil below from this cause. In one of the recent water famines in the East-End of London much of the scarcity of water was attributed to the numerous undiscovered leaks that existed in the pipes underground; and in regard to the waste of water in another district, it was at one time generally understood that the water company found it cheaper to pump more water than to search for small leaks. If then the measure of the water lost by leakage be taken as in some sort a clew to the extent of the risk of fouling of the supply from in-draught during the time when the pressure is turned off, it is clear that a foul subsoil is no slight danger to any town that has an intermittent water supply. It has lately been shown, however, that even while the pipes are flowing full of water an in-draught may take place whenever the speed of flow gives the water a certain momentum and a large quantity of water is being drawn from the pipes in the lower portion of the area supplied; so that even a constant supply is no complete safeguard against the pollution of a water supply when the subsoil of the district to which it is distributed is itself contaminated with excrementitious products. Where, however, as is still the case in many rural districts, the water supply is derived from surface wells, the danger of infection with pathogenic organisms is constant and well recognized.

The best proof of the views here put forward as to the rôle played by water in the distribution of typhoid fever is to be obtained from a consideration of concrete examples, histories of outbreaks which have been shown on investigation to have been set up by the use of specifically polluted water, always bearing in mind, however, the distinction which has already been drawn between the effect of a wholesale implication of a general water supply, an effect usually spoken of as a water epidemic, and that of the repeated implication of separate sources consequent on the micro-organisms having become en-

demic in the places affected and only occasionally gaining access to the water in such quantity as to be effectual producers of disease.

As a mere matter of proof that typhoid fever can be distributed by means of water, those cases in which large water supplies have become infected are the most interesting on account of the large number and varied surroundings of the persons attacked. Where farmsteads become infected with the disease, however clear it may be that the local well is the source and centre from which the infection has been distributed, very often other sanitary deficiencies are present, and it is almost of necessity the case that the people attacked have many other things in common besides the drinking-water. When, however, a town which has, up to the outbreak, been fairly healthy, becomes suddenly or rapidly infected, when the disease attacks people of different classes of society, people whose surroundings differ, and who dwell in different parts of the town, when the one thing that can be discovered common to those who suffer is the water from a given source, and especially when people who get their water from other sources do not suffer, or suffer in markedly less degree, then we may be said to have proof that the water has been the vehicle by which the disease has been distributed.

In August, 1867, an outbreak of typhoid fever began in Guilford, which before it ended affected five hundred persons and caused twenty-one deaths. A new well had been sunk through a porous stratum of chalk, and in close proximity to various sewers, one of which was found to leak in several places, almost certainly polluting the well. On a particular day, and on that day only, houses in a certain part of the town were supplied from a high-level reservoir filled from this well. In the first fortnight of the epidemic all but a few (less than a dozen) of the one hundred and fifty cases that occurred were among the consumers of this high-level supply, and even of the few exceptions three were known to have drunk freely of the implicated water. As is common where local sanitation is not perfect the disease afterwards became more diffused, but during the whole period of its epidemicity it was almost exclusively confined to the part of the town corresponding with the high level section of the water service. People of all classes were affected.

An outbreak of fever among the students at Caius College, Cambridge, although affecting a very much smaller number of persons, is of interest from the fact that the source of the infection as well as the mode of its distribution could be discovered. The incidence of the fever in this case was wholly upon those students who were resident within the college (at Cambridge many of the students reside in lodgings outside the colleges), and a large majority of the cases oc-

curred among those whose rooms were in one particular part of it called Tree Court. The water supply for the college was taken direct from the public mains at six different points, one branch supplying Tree Court and no other part. Now there was a peculiarity about the arrangements of the water-closets; those in the rest of the college had cisterns, while those in Tree Court were supplied direct from the high-pressure main. Although valves were provided which were believed to be capable of preventing any regurgitation of air or water, it was proved that they were inefficient, and that there was a reflux of air when the water at the main was turned off; and on examining a dirty-looking layer which lined the water-pipes this was found to contain nitrogenized organic matter as well as phosphoric acid, showing that liquid filth as well as sewer air had frequently entered the pipes. On further inquiring into the history of the outbreak it was found that one of the closets had been used by an attendant who afterwards developed symptoms of typhoid fever, and that, about a fortnight before the first case occurred among the students, there had been an intermission in the water supply, thus giving an opportunity of in-sucking of foul matter into the pipe, and that certainly just a fortnight before the date of the second, third, and fourth cases there had been another such intermission. It can hardly be doubted that in this case the water arrangements had for long allowed of the pollution of the water supply whenever the supply was turned off, and that so soon as the pollution took place in the form of a specific infection the disease spread among the drinkers.

Between July and October, 1887, in a small town called Mountain Ash, there were 518 cases of typhoid fever, 88 per cent. of which occurred in an area the water supply of which was derived from one main, beyond a point where it was afterwards shown to be leaky and to have been recklessly laid "immediately above, alongside, and even through old rubble drains." At this spot the water-main received into its interior liquid filth from the soil and the sewer whenever the supply was turned off and the interior pressure removed, and there was reason to believe that even when "running full" a certain amount of "in-sucking" of this foul material took place. Mr. Spear, who reported on the case for the Local Government Board, says: "At any time of intermission it is plain that the leaky water-pipes were at liberty to discharge their contents through any opening at a lower level, and that they would convey not only such water as remained in them, but those matters also which entered at the points of leakage. In short, the leaky pipes would act as so many means of draining the ground in which they were placed. . . . Intermission of water-current, however, is not by any means essential for the introduction

of foreign matter into water-pipes. Under various physical conditions very powerful in-suction of external matters into a full-flowing water-pipe can take place." This is a matter of great importance in regard to the nature of the ground through which water-pipes are laid.

An outbreak which occurred at Over Darwen, in 1874, is of great interest from the extraordinary severity of the attack, its suddenness, and its definite connection with a known source of water pollution. The case was reported on for the Local Government Board by Dr. Stevens. Out of a population of 21,273 inhabitants, 2,035 persons were affected with the disease within a very short time, some 1,500 cases coming under treatment within a space of three weeks. The generally dirty condition of the town no doubt greatly conduced to the continuance of the disease after so many foci of infection had been set up, but the sudden and universal outbreak showed its connection with the water supply. It attacked all classes of dwellings, all parts of the town, and houses very differently circumstanced in regard to filth conditions. The water supply was the only condition common to the whole town. On inquiry it was found that the first case, which was an imported one, occurred at a house some distance from the town. It was found, moreover, that the drain from this house, into which the excreta of the patient were thrown, crossed the water-main, that the drain was blocked, that cement around it had given way, that the water conduit was defective at that point, and that, as a fact, the contents of the drain were sucked freely into the water-pipes supplying the town.

An even more definitely proved case was the outbreak which took place at Redhill and Caterham in 1879. A workman employed in an adit between two deep wells belonging to the Caterham waterworks became affected with typhoid fever, but did not at once leave his work. While thus employed he contaminated the workings by the specific infection contained in his evacuations, which were copious and frequent. The epidemic which followed, save for a few secondary cases which began later, was exclusively confined to persons using the water supplied by this company, while large populations closely adjacent to the affected districts, but drinking other water, wholly escaped the fever. The number of persons affected amounted to three hundred and fifty-two. The workman who was the source of the infection continued at his post for a fortnight after he became ill, and after an interval of a fortnight the attacks became general and began to die away after the man ceased work.

The infection of a great river naturally stands on a very different footing from such cases as have so far been mentioned, in that the infection is likely to be much less concentrated, and its incidence on

different communities to be modified in varying degrees according to the treatment to which the water is subjected in the course of its distribution.

The possible, nay probable, connection of typhoid fever in London with the condition of the water supply has already been alluded to. A far more important example, however, of river-borne diffusion of infection is to be found in the history of certain outbreaks, or rather variations in the prevalence, of fever among the inhabitants of certain districts in the Tees Valley supplied with water from that river. This case also is of interest as illustrating the method adopted for demonstrating the influence of an infected water supply upon a population when the area is so great, and the numbers involved are so large, that no method but the statistical is available for the purpose. The investigation was carefully made and very completely reported on by Dr. Barry, on behalf of the Local Government Board. Two distinct epidemics were dealt with, each of six weeks' duration, the first from September 7th to October 18th, 1890, the second from December 28th, 1890, to February 7th, 1891. The whole area dealt with was one of 706,020 acres, or 1,103 square miles, containing half a million people in ten registration districts, and comprising thirty-two separate sanitary areas. In the two epidemics 1,463 cases of typhoid fever were heard of, and of these 1,334, or 91 per cent., occurred among a population of just over 250,000 persons, living in three of the ten registration districts; the rates of attack per 10,000 being 29 and 24 respectively in the two epidemics within the three districts mentioned, while in the remaining seven districts, having a population almost identical in point of numbers, the attack rate was but 3.5 and 1.5 per 10,000 in the two epidemics respectively. In the matter of fever deaths also this special area had rates in the one epidemic three times, and in the other five times, greater than were current in the other seven districts which made up the rest of the area in question.

Taking, however, the sanitary areas, which are smaller in size than the registration districts, it was found that of the whole thirty-two only ten had excess of attack rate and that of these nine lay within the three registration districts already referred to as having an excessive amount of fever; so that whichever way the matter was looked at, whether by registration districts or by sanitary areas, certain portions were separated from the rest by the excessive incidence of typhoid fever upon them. Judged either by attack or death-rates, the exceptional incidence on this special area was heaviest in the second epidemic, which took place at a season when typhoid fever is not apt to be prevalent in this country.

Although Dr. Barry in his report is able to lay bare many glaring insanitary conditions in the district referred to, he was not able to discover any community of sanitary circumstance running through them other than the water supply. In this, however, he found a point in which all the ten excessively invaded districts were alike, for they all drank Tees water, distributed after a process of sand filtration through the works of the Darlington Corporation or the Stockton and Middlesbrough Water Board. Among the 219,435 persons consuming Tees water, the attack rates were 33 and 28 per 10,000, in the two epidemics, while among the 284,181 persons who drank other water, the attack rates were but 3 and 1 per 10,000 respectively. Thus, combining the two epidemics, the remarkable fact came out that the liability to be attacked by typhoid fever was fifteen times greater among the people who inhabited districts supplied with Tees water than among those in districts deriving their water supply from other sources.

Dr. Barry's description of the condition of the river above where water-works derived their supplies is sufficient to explain this excessive incidence of fever upon the drinkers of the Tees water. We read of some twenty villages and hamlets, and of the town of Barnard Castle, draining to the river, of washings of highly manured lands, drainage of graveyards and farmhouses, of privies, urinals, and water-closets, along the foreshore, and of "loads of stinking refuse" deposited on the side of the river aiding in its pollution, especially in time of flood. Nothing was wanted but a flood to wash all these accumulations into the river, and, as a fact, shortly before each of the epidemics which are dealt with a flood did take place; one epidemic being preceded by a "much flooded" condition of the river, the other by an "an eight-foot flood" due to melting snow. In commenting on this report Dr. Thorne Thorne says: "Seldom if ever has a case of fouling of water intended for human consumption, so gross or so persistently maintained, come within the cognizance of the medical department; and seldom, if ever, has the proof of the relation of the use of water so befouled to wholesale occurrence of enteric fever been more obvious and patent."

What is often called milk typhoid is generally only water-borne typhoid finally distributed by means of milk. Either in consequence of the milk-cans being washed in polluted water, or from the direct addition of such water to the milk itself, the milk becomes the vehicle by which the infection is distributed, and thus it happens that the prominent peculiarity of the epidemics depending on this cause is to be found in their location, which usually, at first, coincides with that of the "beat" of one or more milk dealers. One of the first cases of

this kind which was investigated by the medical officer to the Local Government Board, namely, that which took place in Marylebone in 1873, is one of the most interesting from the completeness with which the infection was traced back to the milk, and back from the milk to the use of polluted water from a certain well, and back from that well to the excreta of a patient who was suffering from typhoid fever. In all two hundred and forty-four persons were affected. All the cases occurred in the nine weeks ending August 30th, and within a circumscribed area, and nine-tenths of the cases were in households consuming milk from a particular dairy. Wherever this milk was distributed there the cases of typhoid fever forming the outbreak were also distributed. Where the milk stopped short, there, as a rule, the cases stopped short also. The disease picked out the streets in which the milk was distributed and also the houses where the milk was taken. On one of the farms, situated in Buckinghamshire, which supplied this dairy company, water for dairy purposes was obtained from a well in a yard adjoining the farmhouse. On June 8th the occupier of the farm died suddenly of ambulant typhoid fever. The stools and chamber slops from this patient were, as a preventive measure, buried in an ash-heap, but the position of the ash-heap was such that its soakings must have found their way into the well used for dairy purposes. A heavy rainfall on June 29th probably assisted to wash the infected soakings more copiously into the well, and the water from this well was used cold for the cleansing of dairy vessels—used simply as taken from the well. In regard to the partial invasion of some of the houses supplied from the dairy, it should be noted that while the particular farm in question supplied only about one-sixth of the milk distributed by the dairy company, it furnished all the "nursery milk," which when not wanted for this special purpose was mixed with the ordinary milk; and as the customers began to leave town in July, and less and less nursery milk was required, a larger proportion of the implicated supply got into use for ordinary purposes. Inquiry tended to show that the ordinary milk only became infected to such an extent as "nursery milk" might have become mixed with it.

During July and August, 1878, an outbreak of typhoid fever occurred in Bristol, and affected one hundred and thirty-eight individuals, of whom twelve died. The outbreak was strictly confined to persons who drank milk from one particular farm, these persons being the customers of several retailers all of whom, without exception, were supplied from this farm. Now, on this farm the closets used by the dairy farmer's family discharged by a common drain into a cesspool, situated twenty-five feet from the well. The cesspool was over-

flowing in all directions, and its contents were traced distinctly into the well. The well-water was the only water for domestic use on the farm. In June a young lady convalescing of typhoid fever spent some time at the farm for change of air. Her evacuations (no doubt still infectious) passed into the common privy. It is not necessary to multiply these cases. A large number of examples of milk infection are investigated every year by the officers of the Local Government Board, and their history, although showing great variety in details, always comes back to the same thing—some insanitary arrangement, either on the farm, or in the dairy, or in the shop of the milk dealer, going on perhaps for a long time without declaring itself or apparently doing any harm, and then, on the occurrence of a case of typhoid fever, by which the pollution takes on a specific taint, ending in a rapid distribution of the infection, widespread among the customers of the dairy, but more or less strictly limited to them.

It is to be noted, however, that so-called milk epidemics are sometimes not quite so strictly demarcated as one might expect to be the case; a fact which is explained by the habits of the milkmen. No one can go through the streets in the early morning without observing that, whatever rules may be laid down by the companies, there is a considerable surreptitious sale of milk by the milkmen to persons who could never be traced, and that not infrequently exchanges of milk take place. It is easy then to understand how it is that milk epidemics occasionally overlap the "beat" of the milk dealer whose supply is proved to have become infected.

Cholera.

The proof that cholera is a water-borne disease depends on the same line of argument as holds good in the case of typhoid fever, but it will be observed that there is much in its history to indicate that the dose of the infection which is required to set up cholera is much smaller than is necessary to give rise to typhoid fever. It will also be observed that although there is every reason to believe that the microbe of cholera, like that of typhoid fever, is able to live as a saprophyte outside the body, such external growth occurs only within much narrower limits and under a much less wide range of surroundings than is the case in typhoid fever, and that among these circumstances temperature is a matter of great moment, so that while typhoid fever can maintain its position as an endemic disease in temperate climates, cholera, even when so implanted in such latitudes as to become virulently epidemic, is but an exotic and soon dies out.

The real home of cholera comprises in fact a very limited portion of the earth's surface, while in regard to typhoid fever it may be said

that wherever there is dirt, polluted water supply, and carelessness in the disposal of excreta, there it can make itself a home, can maintain its existence, and can become endemic. In regard to both diseases alike, however, it will be found that the infection always goes in at the mouth, and that if care be taken to let nothing enter the mouth but what is clean, the charmed circle in which the microbe, whether of cholera or typhoid fever, passes from one phase of its existence to another, is broken, and that not only as regards the individual, but equally as regards the locality, the disease dies out.

Asiatic cholera is a specific, communicable disease, which is endemic in certain portions of India, and perhaps in some other places, and, although usually confined to those parts, at times becomes diffused in the form of widespread epidemics throughout the rest of the world. Its mortality is very great, especially in the early part of every epidemic. On the average probably about fifty per cent. of those who are attacked die, but this figure by no means expresses the mortality when the disease first attacks a fresh place, more especially when the circumstances of the attack are such that the infectious material is distributed in considerable quantity and is swallowed at the right moment.

There is every reason to believe that cholera is due to a specific organism, the comma bacillus of Koch, or, in more exact language, the cholera vibrio, and for the purposes of this article this microorganism will be accepted as the cause of cholera. It is to be noted, however, that the dependence of cholera on an organism of some sort, an organism which multiplies within the intestines of the patient, which is discharged with his evacuations, which lives in warm damp soil, in water, in milk, and on the damp surfaces of various kinds of food, which forms a *contagium vivum*, and which ultimately, being swallowed, sets up the disease again in another patient, is demonstrated by evidence quite outside the ordinary proofs of the bacteriologist; and that clinical and epidemiological facts in regard to cholera showed its dependence on such a *contagium vivum*, a growing, living thing, long before the bacteriologist entered upon the field. It must, however, be recognized what strong testimony is borne to the truth of the bacillary hypothesis by the fact that clinical, epidemiological, and bacteriological researches, all alike lead to the same results, although taking such very different routes.

Interesting then as is the fact of the association of cholera with the cholera vibrio, as shown by Koch and since confirmed by numerous observers, it is not on that fact alone that epidemiologists depend when they assert that cholera is a disease which is carried by man and is spread by water.

Nevertheless the knowledge gained in the bacteriological laboratory in regard to the life history of many microbes, and especially what has been learned as to the variability of their pathogenic virulence, is of the greatest importance and is of real help in explaining much that is very dark in regard to the epidemiology of cholera; for simple as it may seem to assume that a man who swallows comma bacilli becomes affected by cholera in consequence of their multiplication within him and the consequent production of those toxic substances which give rise to the symptoms of the disease, it is by no means easy to explain why in some years and in some seasons an epidemic should arise and should spread, while in other years and at other seasons, notwithstanding the prevalence of the disease, it should not extend beyond its ordinary habitat unless it be admitted that under certain circumstances the virulence of the organism is much greater than under others. What these circumstances are, will have to be decided by clinical observation on the large scale in places where the disease is endemic, or in the course of actual epidemics, rather than in the bacteriological laboratory.

The facts worked out in the laboratory are, however, of very considerable interest, and tend largely to explain many of the curiosities —the dark patches—in the epidemiology of cholera.

The cholera vibrio is a non-spore-forming organism, and thus has no means of protecting itself from deleterious agencies. It can then only persist where the surroundings are fitted for its life.

The temperature most favorable for its growth is between 35° and 38° C. It will grow, however, although more slowly, at a temperature as low as 17° C., but under 16° C. no growth can be perceived. It is not destroyed, however, even by freezing; but at a temperature of 65° C. it is soon killed. Although when growing as a parasite it is probably an anaërobic organism, it is strictly aërobic in the laboratory, its development ceasing if its supply of oxygen is cut off. A temporary exposure to carbonic acid does not kill it, but while exposed to such an atmosphere it ceases to grow.

One of the most interesting traits in its cultural character is its intolerance of acids. In neutral or slightly alkaline media it flourishes best, but its development is at once arrested in the presence of free hydrochloric acid.

A peculiarity of its growth which may have some relation to the natural history of the disease is that while its development in a suitable medium is at first very rapid, this quickly reaches its maximum, soon after which degeneration begins, the bacilli becoming altered in appearance as well as losing their power of rapid multiplication.

As a result it is found that when the cholera vibrio is present

along with other bacteria under conditions favorable to growth, it at first increases much more rapidly than the rest, so that it is easy for a time to imagine that one has to do with a pure culture, but after two or three days the vibrios die and the other organisms take their place.

The cholera vibrio then is a facultative parasite, an organism which while a parasite of man is capable also of growing outside the human body amid conditions found in nature, and not merely in the artificial conditions of the laboratory. It has been isolated from choleraic dejecta which have been kept for fifteen days, according to Gruber; fifty-two days, according to Karlinski; one hundred and sixty-three days, and even occasionally after eight months, according to Dunbar. In ordinary milk or on fruit or fish it may survive for several days, while from flies which had been fed on choleraic material the vibrios could be separated after fourteen days. "In water they remain alive for many days; in sterile distilled water for seventy-three days to a year; in sterile well-water for months, but in unsterilized water for from four to twenty-five days; Örgel indeed succeeded in keeping them alive in ordinary Elbe water for almost a year" (Allbutt's "System of Medicine").

It appears probable, however, that comparatively slight differences in the chemical composition or in the physical condition of the water have a considerable influence on the vitality and power of multiplication of the bacilli, for experiments with tank water in India have given very different results on this point, the organisms sometimes multiplying rapidly and at other times as rapidly dying. According to Koch the vibrios have retained their vitality in ordinary spring and well water for thirty days, whereas in water mixed with sewage, as it existed in some of the canals of Berlin, they died much more rapidly; but it should be stated that the observations of different observers on the vitality of the cholera vibrios vary so greatly that it is impossible to say more than that there is plenty of evidence to show that they can retain their vitality both in water and in soil quite long enough to account for most of the ordinary phenomena connected with the transmission of the disease from man to man.

There is, on the other hand, plenty of evidence that the cholera vibrio is pretty rapidly killed by drying, and that it is extremely susceptible to the effect of acids, which quickly inhibit its growth or actually kill it. Abbott says: "The spirillum of Asiatic cholera, while possessing the power of producing in human beings one of the most rapidly fatal forms of disease with which we are acquainted, is still one of the least resistant of the pathogenic organisms known to us. Under conditions most favorable to its growth its development is self-

limited; it is conspicuously susceptible to acids, alkalies, other chemical disinfectants, and heat; but when partly dried upon clothing, food, or other objects, it may retain its vitality for a relatively long period of time, and it is more than probable that it is in this way that the disease is often carried from points in which it is epidemic or endemic into localities that are free from the disease."

It is by the study of instances in which cholera has been introduced into localities which are usually free from the disease, and by watching its behavior when so introduced, observing the conditions under which it can maintain its hold and comparing them with those in which outbreaks, however virulent, die down and come to nothing, that the etiology of cholera can be best investigated. However great the advantages offered by India, or such parts of India as form the endemic home of cholera, for the study of that disease, by virtue of the large number of cases which come under observation, these places by no means form the best field for the investigation of its etiology and epidemiology. The possible causes of any given outbreak are so many, and the modes in which the infection might be introduced are so numerous, that even an approximation towards certainty in regard to origin is very difficult to attain.

Where, however, the disease is an exotic, where the chances against the simultaneous introduction of the disease by different routes are almost infinitely great, and where the outbreak affects so small a number of persons that the history of each case can be individually inquired into, far greater opportunities are offered for ascertaining the manner in which the infection has been introduced, tracing the progress of the epidemic, and observing the mode in which the infective material has been carried from case to case. This no doubt is the reason why the few European epidemics have seemed so much more fruitful of knowledge than the almost constant opportunities for investigation offered in the endemic home of cholera in India. In any case the fact remains that notwithstanding all the work which had been bestowed upon the study of the disease, and all the guesses at truth which had been indulged in in regard to its origin and mode of spread, in the wide field offered by India, it is to the study by Dr. Snow of a small outbreak of cholera among a limited number of people in London, to his careful tracing out of the history of each person involved, and to his acumen in recognizing that, whatever else they had done, each sufferer had partaken of the water drawn from a certain pump, that we owe the demonstration of the fact that cholera is a water-borne disease.

The history of the earlier epidemics of cholera in England, culminating in the proof of the association of the disease with the drink-

ing of specifically infected water afforded by the case of the Broad Street pump, is worth recording. The following account is abstracted from an address on "Water-borne Cholera" by Ernest Hart:

"Cholera first appeared in England in October, 1831, and between that time and the summer of 1833 it ruthlessly ravaged various parts of the kingdom. No accurate history of the epidemic exists, and there are no reliable statistics respecting it, as the present system of registering the causes of death had not then been established. But in places in Great Britain having an aggregate population of less than 5,250,000, the deaths of 31,376 persons, and in Ireland of 21,171 persons, were reported through various channels to the Board of Health. In London alone, which then contained a population of little more than 1,500,000, there were 13,144 cholera attacks, and 6,729 deaths during eighteen months; that is to say, 1 person out of every 117 was attacked by the disease, while 1 in every 250 died. The epidemic filled the people with consternation, and took the medical profession by surprise. Its characteristics were unfamiliar and unaccountable, and its extension was so sudden and mysterious that it was popularly looked upon as a visitation of Providence beyond human control. A consultative Board of Health was established, and the Privy Council circulated rules and regulations, which, though far from complete, contained much sound advice. It was pointed out that the disease had special affinity for the poor, ill-fed, unhealthy parts of the population, especially those persons of drunken, irregular life, and those districts which were unclean, ill-ventilated, and crowded. General cleanliness was enjoined, the provision of special hospitals was advised, and strict quarantine was sought to be enforced. But the most active medium of its epidemic extension—namely, water—seems to have received little thought. The epidemic of 1832, however, set men thinking, and like every succeeding epidemic gave a great impetus to sanitary reform. Before the next great invasion of this country by cholera in 1848, a growing tendency towards improvement in sanitation was distinctly noticeable.

"In September, 1848, cases of cholera occurred in Hull, and were soon followed by outbreaks at Edinburgh, Leith, Sunderland, and elsewhere. It rapidly overran the whole country, and before it had disappeared in epidemic form towards the close of 1849, 53,293 of the English people had died from it, and 18,887 had died from diarrhœa, out of a population of some 17,564,656 living in a great variety of circumstances. It was in August, 1849, while this epidemic was running its course, that Snow cast a strong light on the spread of cholera by propounding his theory that a most important way in which the disease may be widely disseminated is 'by the emptying

of sewers into the drinking-water of the community.' As far as his inquiries had extended he had found that in most towns in which the malady had prevailed to an unusual extent this means of its communication had existed. He pointed out, for instance, that the joint town of Dumfries and Maxwelltown, not usually an unhealthy place, had been visited by cholera both in 1832 and at the close of 1848 with extreme severity. On the latter occasion the deaths were 317 in Dumfries and 114 in Maxwelltown, being 431 in a population of 14,000. The inhabitants drank the water of the Nith, a river into which the sewers emptied themselves, the contents floating afterwards to and fro with the tide. Glasgow, which had been visited severely with the malady, was supplied with water from the Clyde, by means of an establishment situated a little way from the town, higher up the stream, and the water was professedly filtered; but, as the Clyde is a tidal river in that part of its course, the contents of the sewers would be washed up the stream, and the supply of water could not be altogether free from contamination. Again, he pointed out that in 1832 the cholera was much more prevalent in the south and east districts of London, which were supplied with water from the Thames and the Lee where those rivers were much contaminated by the sewers, than in the other parts of the metropolis differently supplied. And this he observed was precisely what again occurred in 1849. It may here be mentioned that in 1849, and for a few years later, none of the London water companies obtained their water higher up the Thames than Vauxhall Bridge, above which point the river received an ever-increasing amount of sewage.

"But apart from the water companies, there were a great many pumps supplied by wells in use in the metropolis. On investigating a sudden and severe outbreak of cholera in Surrey Buildings, Horsleydown, Dr. Snow found that a certain well in use by the patients had been exposed to direct pollution by the dejections of earlier patients. A very similar state of affairs was found at Albion Terrace, Wandsworth Road, where a number of cholera cases occurred almost simultaneously. In that instance there were no data for showing how the disease was probably communicated to the first patients, but it was two or three days afterwards, when the evacuations from these patients must have entered the drains having a communication with the water supplied to all the houses, that other persons were attacked, and in two days more the disease prevailed to an alarming extent.' This explanation of the outbreak was disputed at the time, but Dr. Snow pointed out that 'the only special and peculiar cause connected with the great calamity which befell the inhabitants of these houses was the state of the water, which was followed by the

cholera in almost every house to which it extended, while all the surrounding houses were quite free from the disease.'

"His theory of the whole epidemic of 1848–49 was that the cholera matter was brought to London by patients from Hamburg, that it was multiplied by infected persons, that the infectious sewage matter found its way partly through soil into the wells, and partly through sewers into the Thames and Lee, from which a portion of the water supply of London was derived. This theory was adversely criticised in a report by Drs. Baly and Gull to the London College of Physicians in 1850. Dr. Snow had not long to wait for an opportunity of putting his theory to the test. In the early part of the summer of 1854 cholera had obtained a foothold in London. One special outbreak which occurred in the parish of St. James', Westminster, during that epidemic is almost of historic importance, as it was the first instance in which the agency of water as a disseminator of cholera was clearly demonstrated. The first death in the parish was recorded early in August, and throughout that month a few deaths were recorded each week. But during the week ending September 2d, 78 deaths were registered; in the next week there were 287 deaths, in the following week there were 67, and then the mortality as quickly subsided as it had risen. But before it had disappeared at the beginning of November, some 700 fatal attacks had occurred in this single parish; that is to say, 22 out of every 1,000 persons living in the parish had died of the disease within three months. In the excitement of the moment various causes were assigned for this mysterious and sudden outburst. Some accused the ancient pest field in the parish, where during the great plague the dead had been buried by the hundred, of casting forth the disease germs buried there nearly two hundred years previously. Others laid the blame on the unflushed and defectively ventilated sewers; while others, again, found sufficient cause in the extreme heat of the weather. But no satisfactory solution of the mystery presented itself until Dr. Snow was called in to examine the water supplies.

"On studying the record of the deaths, Dr. Snow found that nearly all of those registered in the first week of the outbreak had taken place within a short distance of the parish pump in Broad Street; and that of 73 deaths in the locality around this pump, 61 were found to have been of persons who used to drink the water from that particular pump. Pursuing his inquiries, he found that in a factory in the neighborhood, where the water was always used, 18 out of the 200 workpeople died. On the other hand, in an adjoining brewery in Broad Street, where water from that pump was never used, not one of the 70 workmen employed suffered from the disease.

In another case a gentleman came from Brighton to see his brother, who was attacked by cholera in a house near the pump. On his arrival he found his brother dead, but he did not see the body. He remained only twenty minutes in the house, and after partaking of a hasty lunch, including some brandy and water (the water being from the Broad Street pump) he proceeded to Pentonville, where he was attacked by cholera during the following day and was dead within twenty-four hours. In yet another case, a lady living at Hampstead was in the habit of having brought to her daily a large bottle of water from the Broad Street pump, as she had a preference for it, the water being both cool and sparkling as sewage-polluted water often is. The water was taken to her as usual on August 31st, she drank of it, was seized with cholera on the next day, and died within twenty-four hours. A niece who was on a visit to this lady also drank of the water, returned to her residence in a high healthy part of Islington, was attacked with cholera, and died also. In all these cases the water was used cold and unboiled. Many dismal incidents such as these were discovered both by Dr. Snow and by the Rev. Mr. Whitehead, who conducted an independent investigation and showed the complicity of this well water with the outbreak. On following up the clew it was found that the pump immediately adjoined the house, No. 40 Broad Street; and on the drains of that house being opened a filthy condition of things was disclosed. There was a cesspool under a common privy, within three feet of the well and at a higher level than that of the water in the well. The walls of the cesspool were rotten, and the contents could leak into the surrounding soil. The walls of the well were also found to be rotten, and there was distinct evidence of the cesspool contents having for a long time leaked into the well. Further investigation also disclosed the fact that on August 28th a child, aged five months, living in this house, was attacked with what was registered as diarrhœa, and died on September 2d. The symptoms of this child's illness, however, were distinctly choleraic.

"This ghastly experiment fortunately bore good fruit. The more practical of our sanitarians realized its bearings, and the purity and protection of our water supplies received more attention. The first step was the abolition in the metropolis of such dangerous shallow wells as that in Broad Street; wells which, in the words of Sir John Simon, contained evidence that 'they represented the drainage of a great manure bed.' "

The distribution of the cholera poison by means of well-water, comparatively small in quantity and infected as directly as was the case in the instance just recorded, must not be taken as indicating the limits of capacity for evil possessed by water as a carrier of the dis-

ease in question. It has already been mentioned that there is reason for believing that a much smaller dose of the vibrios of cholera may be capable of inducing the disease than is the case in regard to the bacilli of typhoid fever. This may possibly have to do with the extraordinary power of rapid self-multiplication displayed by the cholera vibrio during the first few days after its inoculation into a medium fitted for its growth. At any rate in some of the water epidemics which have been recorded the actual amount of infective material introduced into the water supply must have been very small indeed. Of this the outbreak of cholera in the east of London in 1866 may be taken as an example. Ernest Hart says:

"The disease appeared in London in the last week of June, when 6 deaths were registered. During the succeeding weeks there were 14, 32, 346, 904, 1,053, 781, 455, 265 deaths, and then the mortality gradually declined, but before the first week of December 5,915 deaths had been registered. Of these, 4,276 occurred in the east districts of the metropolis and adjacent suburban districts of West Ham and Stratford. It was in these districts that the rapid and unexampled development of the outbreak occurred.

"Early in the outbreak I was struck by its incidence on the area supplied with water by the East London Water Company, and I felt confident it could only be due to a sudden specific pollution of the water supply. Acting on behalf of a great medical journal I dispatched the late Mr. J. Netten Radcliffe (who had not then become attached to the medical department of the Privy Council) to investigate the matter. At first, of course, he was met with a blank denial on the part of the water company that anything had occurred in connection with their water supply which could explain the distribution of cholera; a refusal to accept any such denial, and a patient investigation, in which the officials gave all necessary aid, though under protest, at last made it plain that owing to changes having been made in their filtering apparatus the company had sent out for a few days unfiltered water, or water in a very partially filtered state, direct from the river Lee. Subsequent inquiry proved that just at that moment the waters of the Lee had been infected with choleraic discharges from a cottage whose sewers were connected with the river, and in which a family had come to reside who had reached Southampton infected with cholera, and were allowed to pass on after they were supposed to have recovered."

As an illustration of the spread of cholera by means of water drawn from a river of much larger size and presumably containing the poison in an even more dilute form, the instance of Hamburg may be cited.

Cholera broke out in Hamburg about August 16th, 1892, and soon became widely diffused in the city and port, 16,956 attacks and 8,605 deaths occurring between August 16th and the middle of November. This was the most severe epidemic from which Hamburg had suffered, although cholera had prevailed in that city on sixteen occasions. The infection was widely distributed by means of the sewage-polluted water which was at that time delivered to the population from the River Elbe. Indeed the experience afforded by Hamburg in respect of water serving as the medium for the diffusion of cholera in epidemic form has become historic by reason of the researches of Professor Koch and others, which went to show that, whereas Hamburg, drinking unfiltered Elbe water, drawn from a point above the sewer outfalls, but still liable to occasional sewage pollution by reason of tidal action, suffered from epidemic cholera on a scale of exceptional magnitude, the adjacent town of Altona, practically forming with Hamburg one continuous community, but drinking filtered water, suffered only in a very minor degree, although its water was drawn from the same river, and at a point below that at which it was befouled by the sewage of well-nigh eight hundred thousand people resident in Hamburg and Altona.

According to Professor Koch, the remarkable immunity of Altona was due to the fact that the Altona water, which was filtered through sand and gravel, was so far freed from the micro-organisms suspended in it by means of the slimy layer of mud, etc., which formed on the surface of the filtering area, as to reduce the risk of mischief to a minimum.

In regard to this epidemic Professor Koch, in a paper on "Wasserfiltration und Cholera," says: "Most surprising were the conditions of the cholera epidemic along the boundary between Hamburg and Altona. On both sides of the boundary the conditions of soil, buildings, sewerage, population, everything, in short, of importance in this respect were the same, and yet the cholera went right up to the boundary of Altona and there stopped. In one street, which for a long way forms the boundary, there was cholera on the Hamburg side whereas the Altona side was free from it. Indeed in the case of a group of houses on the so-called Hamburger Platz the cholera marked out the boundary better than any one having the map of the frontier between Hamburg and Altona before him could have done. The cholera marked not only the political boundary but even the boundary of the water supply between the two towns. The group of houses referred to, which is thickly populated by families of the working classes, belongs to Hamburg, but is supplied with water from Altona; and it remained completely free from cholera, whereas

all around, on the Hamburg territory, there were numerous cases of disease and death. Here we have to do with a kind of experiment which was performed on a population of over one hundred thousand, but which, in spite of its immense proportions, complied with all the conditions which one requires from an exact and perfect experiment in a laboratory. In two great populations nearly all the factors are the same—one only is different, and that the water supply. The population supplied with unfiltered water from the Elbe is seriously visited by cholera; the population supplied with filtered water is only visited by the disease to a very small extent."

As an illustration of manner in which peculiarities in the area of distribution of cholera, among the inhabitants of a city, depend upon peculiarities in the arrangements in regard to water supply, the case of Naples may be cited. During the prevalence of cholera in that city in 1884, and indeed in nearly all preceding epidemics, contrary to the customary rule in cholera epidemics in most parts of the world, persons dwelling in the upper stories of the houses suffered the most severely from the disease.

The reason of this is pointed out by Dr. Shakespeare in his work on cholera. He points out that the houses of the poor quarters are many stories in height, and are tenanted by families who live in flats. The upper flats are constructed upon the same plan as the lower ones, the kitchens of all being directly over each other. The water-closets, when they exist, usually occupy one corner of the kitchen, and connect by untrapped pipes with the main perpendicular drain, which leads to a *pozzo nero*, or sort of filth receptacle, in the basement of the house. It is usually only the overflow of the fluid contents of the *pozzo nero* which enters the main house drain and passes to the street sewer. The walls of the *pozzi neri* are usually very imperfectly, or not at all cemented, the floor of the sink being formed by the porous earth. The solid accumulations in the *pozzi neri* are not often removed more than once a year. In most of the large houses there was, at least until 1885, as already stated, a very peculiar individual provision for water. Running water flows in masonry trenches from house to house, ordinarily a little underground. In the course of the trench, as it passes beneath the house, there is a cistern sunk beneath the bottom of the trench, in order to form a species of water reservoir for household purposes. This reservoir is usually located in the part of the building immediately under the kitchens of the various floors, and is in communication with them by means of a bucket attached to a rope which runs over a pulley at the top of the house, so that the occupants of the various stories can draw the water without the necessity of descending to the ground floor. The loca-

tion of these reservoirs is therefore frequently in close proximity to that of the *pozzi neri*, and, from what has already been said of the construction of these *pozzi neri*, it is easily understood how filtration from them must unavoidably reach and contaminate the water of the reservoirs. And the fact that the water trench passes from house to house and directly communicates with the reservoirs, explains how, in houses where the *pozzo nero* and the reservoir are quite distinct, the water drawn from the reservoir is often necessarily contaminated by the *pozzi neri* of houses up stream.

Besides this household provision of water, there is also a public supply by means of a comparatively limited number of public fountains in the streets and public squares. The majority of the inhabitants recognize the fact that the water of the public fountains is of a better quality for drinking purposes than that drawn from the reservoir within the houses, and those living on the ground floors and not too far distant from the nearest public fountain habitually resort to the fountain for their drinking-water, using, however, the reservoir water for other domestic purposes. Dr. Shakespeare notes in connection with this practice the curious fact that during the prevalence of cholera in Naples in 1884, and, indeed, in nearly all of the preceding epidemics, persons dwelling in the upper stories suffered the most severely from the disease. The explanation of this fact is patent. The ease with which those people could obtain water from the reservoir, and the inconvenience of resorting to public fountains, caused them to use water which was by far the most likely to be contaminated by cholera discharges.

In addition to the contamination of the reservoir water by cholera discharges which might reach the *pozzo nero*, in not a few instances the reservoir water was further contaminated by the reckless practice of washing linen soiled with choleraic discharges in the trenches of running water beneath the houses.

It is difficult to realize the fact that such a system as this—a system which could scarcely be better designed for the most effectual distribution of disease—was to be found, towards the close of the nineteenth century, in such a populous and important city as Naples. Fortunately the danger was at last recognized in 1884, and in the following year pure water was brought into the city from a mountain stream—the Serino, eighty miles distant—and was very generally distributed through iron pipes under pressure. At the same time the old system of distribution by water trenches coursing beneath the dwellings was, to a great extent, done away with. Neither in 1885 nor in 1886, notwithstanding the existence of cholera in the vicinity and the not infrequent arrival of refugees from cholera-stricken local-

ities, did Naples suffer from even limited epidemic outbreaks of the disease. This was true also of the year 1887, until, in consequence of a break in the new water conduit from the distant mountain stream, recourse for a few days was had very generally to the old water system. At this time there were numerous refugees in the city, as, in fact, there had been for weeks past, from various places in Southern Italy and Sicily, including several suburban towns where cholera was more or less prevalent. Moreover, there were, and had been, almost constantly occurring a few isolated cases of the disease among these refugees, without, however, a local epidemic being produced thereby. But very soon after the interruption of the supply of the Serino water there were one or two quite sharp explosions of local epidemics around some of these cases. The speedy repair of the Serino aqueduct enabled the municipal authorities again to turn on that pure water throughout the city, and, practically coincident with that action, the local epidemics, which had occasioned so much alarm, ceased almost as suddenly as they had begun.

It is interesting in this connection to note that there has been a very marked decrease in the prevalence of enteric and typhus fevers since the introduction of the new water service into Naples.

An epidemic which broke out at Genoa in 1884 is of interest as showing not only that pollution of a water supply may cause a sudden outbreak of cholera, but that cutting off the polluted supply may be followed by a rapid cessation of the epidemic. The following account is condensed from the address on water-borne cholera by Ernest Hart, already quoted:

"The disease reached the city of Genoa in September, 1884, and the severe epidemic which immediately ensued is one of the most interesting and conclusive examples recorded of the spread of cholera by water—by water, moreover, which was of exceptional natural purity until the moment it received the specific infection.

"A few sporadic cases of cholera occurred in Genoa during the first fortnight of September; but immediately following the 21st of that month the disease suddenly and rapidly spread. In every part of the city there were attacks, without distinction of the density of the population, or of social status, or of hygienic conditions or precautions. The dissemination was so general that the first three hundred cases were found to be scattered along one hundred and fifty-eight different streets of the city.

"Early in the epidemic a resident physician, an old friend of mine, telegraphed to me from Genoa: 'Your water theory of cholera at fault. Genoa has a fine supply of pure water from a high mountain source. Cholera has broken out in districts so supplied, and we

have already one hundred cases a day. What is to be done?' I replied by telegraph:—'Cannot be at fault; must be water; cannot be anything else. Examine every foot of your water-pipes, and trace to the supply pipes' source.' Genoa, it may be remarked, is supplied by three aqueducts—the Civic and the Galliera, about fifteen miles long, fed by the River Gorgento, and the Nicolay, about thirteen miles in length and supplied by the River Scrivia. An analysis of the first 50 cases of cholera in the city disclosed the fact that as many as 44 were in houses supplied with Nicolay water; of the 50 succeeding cases, 43 dwelt in houses supplied with Nicolay water; and of the third group of 50 cases, 45 were in houses so supplied. In fact, out of the first 300 cases, as many as 93 per cent. inhabited houses in which the Nicolay water was distributed. Further, although the poorhouse of the town is in a very crowded centre, no case of cholera occurred in it, as the authorities of that institution cut off the Nicolay supply. Again, taking the Via Bianchetti, cases of cholera occurred on the side which was served with Nicolay water, while there was not a case on the other side, which had water from a different source.

"Thus the Nicolay water stood convicted, and on further investigation the mystery was readily solved. Near the beginning of the Nicolay aqueduct is the village of Busalla, and at the time in question some hundreds of workmen, including, there is reason to believe, many refugees from infected localities, were engaged on a new railroad, and are described as living in the most filthy conditions. Cholera broke out at Busalla on September 14th, and several cases thereafter daily occurred until the end of the month. Inquiry disclosed the fact that nearly all the workmen, both the sick and the healthy, had their clothes washed in the Scrivia, or in a tributary of that stream, which supplies the Nicolay aqueduct with its water.

"As soon as these facts were known the mayor of Genoa, with very commendable promptitude and decision, prohibited for a time the distribution of the water of the Nicolay aqueduct, or rather the distribution by that aqueduct of the water of the Scrivia. This was done on September 28th. On September 30th the cases of cholera fell from 64 to 59, and, as already shown, during the succeeding days the number of cases suddenly dropped to 40, 27, 22, 21, followed by a rapid decline to *nil* on October 17th."

It is to be observed that, much as has already been described in regard to typhoid fever, so in the case of cholera, an epidemic which in its mode of onset may be typically characteristic of diffusion by means of water may not die away, as a purely water epidemic tends to do, so soon as the source of pollution of the water supply has been

discovered and removed. Once started, the prevalence of cholera may persist—may in fact persist as long as the conditions continue under which the cholera vibrio can maintain its separate existence and can, even only occasionally, find access to the drinking-water or the food of man. This was markedly the case in the earlier outbreaks of cholera in Europe, and always has been and still is characteristic of the progress of the disease in many parts of India. However definitely cholera might be introduced by an infection of the general water supply, it was maintained by local insanitary conditions, and spread so rapidly under their influence that its original mode of distribution was thoroughly masked.

It will be found, however, that in many of the cases in which cholera is said to have become endemic, and has in fact taken on the endemic type so that it can no longer be traced to any pollution of public water supplies, a careful search into the habits of the people and into the sanitary deficiencies to which the prevalence of cholera may be attributed will show that even these habits and these sanitary deficiencies are effectual in producing cholera, chiefly because they involve the pollution of drinking-water or cooking-water with cholera-infected material; in other words, that the cholera which arises from local insanitary conditions is in most cases as much water-borne, in some part or another of its course from man to man, as is that which occurs in sudden outbursts, affecting large areas, and definitely connected with pollution of public water supply—the form which has earned for itself the term water cholera.

Although this article only professes to deal with cholera so far as it is a water-borne disease, it is here necessary to consider briefly some of the facts which have been learned in regard to the laws which seem to govern its diffusion in India, and in regard to the influences which appear to be at work in setting up those exacerbations of epidemic virulence which enable the disease, which is normally confined to a comparatively small area, to become at times a widespread epidemic pestilence, crossing seas, traversing continents, and carrying destruction in its course around the world.

What is important to observe in this respect is that even in its endemic home in India cholera rises and falls, varying in its prevalence from month to month and from year to year, and that within that area it travels from place to place, not being always present in all places but occurring in outbreaks, and then subsiding much as it does when, as an exotic disease, it affects people in countries not usually liable to its attacks.

Cholera is always essentially the same, and differs only in its degree of virulence and in its opportunities for diffusion.

The main peculiarities of the climate of the part of India in which cholera is constantly endemic are its moisture at certain seasons, its heat, and the existence of a dry season necessitating the use of stored water; while in regard to the social customs of the people by which the prevalence of cholera is maintained, prominence must be given especially to two—first to the frequent ablutions and the constant washings of their clothing (loin cloths) which are customary in the districts in question, by which the water supply, so far as it is kept in tanks, tends to become polluted; and secondly to the great religious bathing festivals, the pilgrimages to which are a frequent means of carrying the disease into fresh districts and setting up fresh centres of infection.

It is then to be noted that so far as climatic influences are concerned—dampness of soil, great changes in the level of subsoil water, great floods washing surface impurities into the water supplies, and the climatic necessity for using stored water—they all have to do more or less with water; and that so far as social customs are concerned they also are related to water and its domestic or personal use.

The physical conditions which seem to influence the tendency of cholera to become endemic in any place have to do with ground water, ground air, rainfall, altitude, temperature, the nature of the soil, and the prevailing sanitary condition. These matters are best studied in India, especially in those parts into which there are frequent opportunities for the reintroduction of the infection. In countries where the disease is exotic, the introduction of the infection is the dominant factor in deciding the occurrence of an outbreak. Where, however, the infection is almost constantly at hand, the conditions of the place in question are chiefly responsible for the result, and by them is decided the question whether the disease shall become prevalent or shall pass away. It would appear from Macnamara that in India there is no universal relation between rise or fall of ground water and the prevalence of cholera. In Lower Bengal the mortality from cholera is as a rule highest during the dry season, from October to May, and throughout the rains the death-rate decreases. At first sight it might appear as if some connection existed between the rise and fall of the ground water and the increase or decrease of cholera in that part. The connection, however, is but incomplete. The maximum of cholera does not coincide with the lowest level of the ground water, nor on the other hand does the alteration of its level seem to be influential in the production of the disease. During December and January the level of the underground water subsides, yet the cholera mortality, instead of rising, falls. Moreover the relation

between conditions of the ground water and prevalence of cholera varies in different parts of India, so that no rule can be deduced in regard to its connection with the spread of the disease.

The relation of water with the soil, so far as the causation of cholera is concerned, would seem not to be so much a matter of the rise and fall of the level of the ground water, as of the production of such a condition of moisture and of aëration of the soil as shall render it a fitting spot for the development of the cholera bacillus. Looked at from this point of view it would appear that the character of the soil as to porosity, power of retaining moisture, and power of absorbing air; the sanitary condition of the place, by which is regulated the amount of organic matter present in the soil; the amount of rainfall, by which is determined the amount of moisture reaching it; the slope and altitude of the area in question, by which are determined the freedom with which the water drains away; and the temperature which prevails in the region at the time—all take a share in the production of the particular condition required, viz., a moist, well-aërated soil, containing a considerable proportion of decomposable organic matter, and maintained at a comparatively high temperature.

In some parts of India, where the soil is always naturally in a fit state for the breeding of the cholera vibrio, the onset of the rains, by which the soil becomes sodden with water and all the air is driven out of its interstices, stops the progress of the disease, while in other regions, which usually have a dry soil, it is not until the rains come that the cholera can take root. There is thus no constant relation between the rains and the cholera. Sometimes the rains produce and sometimes they destroy the conditions necessary for the development of the disease. It is easy also to understand why cholera so often prevails in the neighborhood of rivers; partly from the fact that the rivers are the natural highways of travel and that it is mainly along the lines of travel that infection spreads, but also from the fact that along the banks of rivers there is often just that overcrowding of the population, that accumulation of decomposing matter, and that degree of dampness of the subsoil, which are so conducive to the growth of the micro-organism on which cholera depends.

It would not be a correct view of the matter, however, to look upon the geological and climatic influences as responsible for the persistence of cholera in India. Although the cholera vibrio can live and grow for a time in the soil or in water, there is no reason for believing that it ever takes on permanently or even for any very considerable time this saprophytic form of existence. The climate of India favors its persistence in that by its aid the microbe can easily maintain its existence outside the body, so as to bridge over those

intervals which must usually elapse between its exit from one host and its entry into another; but that is all. It is to the habits and customs of the people that the persistence of cholera is largely due.

The instincts of the Hindus are in favor of cleanliness, and many of the obligations laid upon them by custom and tradition are in essence of good sanitary intent; but as carried out, and as put in practice in many of those parts where cholera is common, they have so far lost their original meaning as to have become instruments for the spread of disease rather than for its prevention.

The custom of indulging in frequent ablutions and daily bathings, although in itself good, tends definitely to evil when water is scanty and the same supply has to be used both for cleansing and for cooking purposes. If possible it is customary for the Hindus to bathe every day, and for the women to do so even oftener, and yet during several months there is no rainfall and they have to trust entirely, both for drinking and bathing, to water which has been stored in tanks. The custom continues although the meaning of it is lost sight of, and thus it happens that in some villages, which are supplied only with tank water, it is the ordinary habit of the natives to use for all culinary purposes water drawn from public tanks in which the villagers bathe and wash their clothes, and around which is accumulated all sorts of filth, including much excrementitious matter. There can be no doubt that the habit of drinking foul water, and the constant risk thereby involved of drinking water which has become polluted with the specific infection of cholera, is the great cause of the constant presence of that disease in India.

In a paper read before the British Medical Association in 1888, Dr. Simpson, medical officer of health for Calcutta, gave a description of that city and the adjacent town of Howrah and their suburbs, dealing especially with their sanitary arrangements. Calcutta to the south of the native town is, he said, well built; the streets are wide and straight; there is a liberal supply of excellent water, the drainage and cleansing are good, and that part of the city compares favorably with the better parts of London. With a few exceptions the northern and native Calcutta is densely crowded, the streets are narrow and irregular, the drainage is bad, only the better and middle classes have a fair supply of water; the poorer class have a very scanty water supply, and depend upon the water in the tanks. The native town is studded with wells and tanks. Neither Howrah with its 100,000 inhabitants nor the suburbs of Calcutta with its 250,000 has any public water supply with the exception of the wells and tanks. As a general rule European residents in Howrah get their water from Calcutta by carriers, and they avoid the well and tank

water. The personal habits of the natives are cleanly. As a religious duty they bathe at least once a day, the women more frequently, and this is done when convenient in the River Hoogly, but generally in the tanks near their houses or huts. The tanks are thus defiled by the excretions of the body, by the washing of dirty clothes, frequently of clothes soiled by excretions of the sick, by human ordure due to the practice of children and others defecating on the banks of the tanks, and by the drainage and soakage from the surrounding huts and houses. Thus the water in the tanks, except during the rainy season, becomes extremely foul, and this is the only water supply practically available for large numbers of the native population.

One may indeed legitimately express astonishment that, with the facilities which exist in such places for the ingestion of the cholera infection, the whole native population is not swept away by the disease. In regard to this it must be remembered that only a certain portion of any community is susceptible to cholera, while there is every reason to believe that a certain degree of immunity to the disease is acquired by those who are constantly exposed to small doses of its infection. Probably this is the explanation of the fact that, heavy as is the loss of life from cholera in those parts which are constantly affected by its ravages, the percentage of mortality (in those years when cholera does attack them) is considerably higher in those places where the disease is only an occasional visitor than in districts where the cholera is constantly endemic.

Although it is now generally admitted that cholera is capable of being diffused by means of water, it so often happens in India that outbreaks occur which the most careful search fails to associate with any deficiency in the arrangements for the water supply, that the view is strongly held by many that the sporadic outbreaks of cholera which are so common in that country must be caused in some other way. Great interest therefore attaches to the researches made of late years by Mr. E. H. Hankin, bacteriologist to the Northwest Provinces of India, who has investigated with minute care several such outbreaks, and to the results he has obtained, in that they tend to show the large part played by water in the etiology even of these sporadic cases, distinctly differentiated as they may seem from the epidemics which arise from wholesale infection of large public water supplies.

In certain cases he was able to trace the infection to the eating of cucumber, and in these cases it was clear that the microbe had obtained access to the skin of the cucumber, as it does also to the skin of the melon, as a result of the extremely foul surroundings in which

these vegetables are grown. But even in these cases the washing of the cucumbers had led to the infection of certain water-vessels in the cookhouses, notwithstanding that the origin of the water had been proved to be good. He has shown also that the skins in which water is usually carried about by the water-carriers may themselves become infected with the cholera vibrio, so that the water distributed by these men may carry infection, although it may have been derived from a perfectly pure source. The Indian cookhouses, moreover, and the habits of the cooks appear to be largely instrumental in the production of a certain class of outbreak not uncommon in India, where sometimes cholera occurs even after the most complete measures have been taken to secure pure water. The following is an example of the kind of investigation which has to be undertaken by a bacteriologist who would get to the root of the matter, and shows how the most obscure cases may turn out, on sufficiently minute inquiry, to have arisen from water-carried infection. The case was published in the *British Medical Journal* for December 26th, 1896, and is as follows:

"On July 13th, 1896, thirteen persons sat down to dinner on a guest night at an officers' mess in Saugor, a station in the Central Provinces. Two days later no fewer than nine of the partakers of the dinner were attacked with severe diarrhœa, vomiting, and prostration, which in three cases developed into typical cholera. Of these three cases, only one recovered. The outbreak in its sanitary aspects was investigated by Brigade-Surgeon-Lieutenant-Colonel Hutcheson, sanitary commissioner to the Central Provinces, assisted by Surgeon-Captain Marks. At the time no other cases of cholera were occurring elsewhere in cantonments, and but little cholera was present in the neighboring town. This isolation of the outbreak might be regarded as adding to the difficulty of supposing that it was ordinary cholera, and it might be suggested that it was an example of ptomain poisoning. The high percentage of those exposed to the infection who were attacked, and the presence of tinned prawns in aspic as an item in the *ménu* of the fatal dinner party, lent color to the idea. But, on the one hand, the existence of a regular incubation period of about two days in every case, the typical choleraic aspect of the symptoms in the severer cases, and the fact that at least one of those attacked had not eaten the tinned prawns, made the conclusion inevitable that the disorder was due in part at least to the cholera microbe.

"A clew to the proximate cause of the outbreak was furnished by the only other case of cholera that occurred in the cantonments at the time. The patient was a servant of one of the guests, and had been employed in the mess on the occasion of the dinner party in question. Owing to his being a Madrassi he could eat European food. Such food could not be eaten by the other servants owing to their caste customs. The Madrassi servant was attacked on July 15th—that is to say, at the same time as the other victims, and died on the same day. It was discovered that he had eaten the remains of a chocolate pud-

ding that had been left over from the dinner. He had not eaten any of the tinned prawns or any other food so far as could be ascertained. That the outbreak was not due to the more ordinary channel of drinking-water was proved by the fact that all the servants in the mess drank from the single well that was in the mess compound, and that with the above exception they all remained in good health; further, the mess was provided with a Pasteur filter, and but few of the members ever drank water. Consequently the investigation threw a strong suspicion on the chocolate pudding. At this stage of the investigation I was called in to see whether the bacteriological test could throw any light on the mode of access of cholera microbes to the chocolate pudding, and on the reason why in this position these microbes exhibited such exceptional virulence.

"A bacteriological examination of everything in the mess-house and mess-house kitchen that was wet resulted in the discovery of the cholera microbe in a fully virulent condition in a sufficiently unexpected position. Such care was being taken, and had been taken, in the sanitation of this kitchen, that all drinking-water was not only boiled but passed through a Pasteur filter. The cholera microbe was found in a degchie of recently boiled water that was standing near the Pasteur filter ready to be poured into it. The water coming from the Pasteur filter naturally was free of cholera. The original water supply whether taken direct from the well or from the bhisti's mussack was found to be free of infection. The same water, whether stored in earthen vessels or in tins or glasses in the mess-house, was in every case found to be free of infection. There is every probability that the water in the degchie had really been boiled, a process which obviously would remove any cholera microbes that might be present, since after a severe outbreak such obvious precautions are not usually neglected. No one had in all probability introduced the infection by taking water out of the degchie by means of an infected vessel, because the degchie was still quite full of water at the time of my visit. It was not likely that the infection had been introduced by means of flies into the water, because the lid was on the degchie, and probably had been there since the degchie had been removed from the fire. Only one channel remains that I can think of by which the water in the degchie is likely to have become infected, namely, from the dishcloth used in carrying it. A degchie, it may be explained, is a cooking-pot without a handle, whose mouth is provided with a projecting rim. The servants usually take hold of this rim on both sides by means of a dishcloth when carrying the degchie about. The lid is merely a concave sheet of metal fitting loosely, and while the degchie was being carried from the kitchen to the pantry the water it contained was almost certain to be splashed up against the dishcloth, and if the dishcloth was infected with cholera microbes, the latter might be introduced into the water. Investigation showed that the clean dishcloths on their return from the wash arrived impregnated with cholera microbes. The mess dhobie was in the habit of washing the dishcloths in a running stream two miles and a half from cantonments, in whose water no cholera microbes could be detected. Surgeon-Captain Marks, who investigated the matter, found that it

was highly improbable that the dishcloths had become infected owing to their having been washed in the same vessel as cholera-infected clothing, both because the dhobie did not use any vessel, but only the running water, and because, so far as could be learned, he only worked for the mess and for a few Europeans who had remained in good health. For some time the source of infection of the dishcloths entirely escaped our search, but at length Surgeon-Captain Marks found that during May and June, that is to say, during the few weeks before the outbreak in the mess, five or six cases of cholera had occurred in some huts situated about thirty yards from the place where the dhobie washed. The drainage from these huts went in the direction of the river, and at length the cholera microbe was detected in sand from near the bank of the river at the place where the dishcloths were usually laid out to dry.

"Though other sources of infection are by no means excluded, the above is the only way by which virulent cholera microbes may have been introduced into the mess at the time of the outbreak in favor of which any positive evidence can be brought forward.

"Assuming that at the time of the outbreak cholera microbes were present on the dishcloths, it is obvious that the chocolate pudding or its constituents may have been infected by any of the vessels used in its preparation having been cleaned by these dishcloths. There is another more direct way in which the infection may have been introduced, depending on the habits of the native cooks. Every cook possesses a piece of muslin through which he strains all sauces, custard, blanc manges, etc. This muslin, owing to its frequent use, is apt to acquire a bad smell. If this becomes too pronounced, the food acquires a disagreeable flavor, and the cook is likely to be fined. In order to avoid this the muslin is occasionally sent to the wash, I suspect, even in cases in which the dishcloths are never thus exposed to the risks of infection with the microbes of water-borne diseases. As will be shown below, the constituents of the chocolate pudding had been strained through such a piece of muslin.

"The question now arises, Why should chocolate pudding be such a dangerous nidus for cholera microbes? An answer to this question may be obtained from a consideration of the method of making it, and of the properties of its constituents. Roughly speaking, it is made as follows:

"First, the contents of a packet of gelatin are dissolved in warm water. The cook then adds to it milk, sugar, and the whites of several eggs. The constituents are well beaten up together, and then strained through a piece of muslin. The mixture is next divided into three portions. To one powdered chocolate is added to produce a brown color; cochineal is added to the next portion, and the third portion is flavored with essence of vanilla, possibly in order to remove the taste of the cook's fingers. A mould is placed in ice. A part of the still warm chocolate-colored portion is poured into the mould. When it has set, some of another colored portion is added. When this has set, more is added, and so on until the mould is full. Thus a pudding of opaque jelly in different colored layers is produced. This is obviously a long process, during which the portions that are

not yet in the mould are kept at a warm temperature, such as tends to aid the growth of microbes, for several hours.

"From the above enumeration of the constituents, it is obviously likely that the chocolate pudding will be a good breeding-place for cholera microbes, and it is possible that the large percentage of attacks in the present instance was due to cholera microbes having been swallowed in enormous quantities. In order to test this possibility, it was obviously necessary to obtain the constituents in a sterile condition, and then to add a measured quantity of cholera microbes, and estimate their rate of reproduction.

"So far as the milk and eggs were concerned, it was necessary to obtain them in a sterile condition without the aid of heat, as boiling might possibly affect their nutritive value. In order to do this some milk was obtained from a disinfected cow, by means of a disinfected milkman with every aseptic precaution. Some of the white of a fresh egg was removed through a hole in a portion of the shell that had been calcined in a blowpipe flame. These two liquids were added to some previously sterilized and dissolved gelatin in a test tube. The mixture was inoculated with a trace of cholera microbes, and it was then found that about twenty thousand of these microbes per cubic centimetre were present. I imitated the cook in keeping the mixture in a warm place, by putting the test tube in an incubator.

"On the following day the cholera microbes had reproduced at such a rate that nine millions were present in every cubic centimetre. This rate of reproduction was not quite so much as I had expected for chocolate pudding, so I suspected that I had made some mistake in the culinary part of the experiment. This I was fortunate enough to detect. I had used the ordinary laboratory gelatin that is used for cultivating microbes. The cook had used the specially purified gelatin that is sold for making jellies and similar nutritious food for invalids. I thereupon repeated my experiment, but using the shop gelatin instead of the other. The mixture was again inoculated, and this time the cholera microbes reproduced with such amazing rapidity that eighteen hours later no less than four hundred million cholera microbes were present per cubic centimetre. The explanation of the difference in the results of the two experiments is extremely simple. The ordinary coarse gelatin that I used in the first experiment is acid in reaction. The other constituents of the chocolate pudding are alkaline or neutral. The mixture has a faint acid reaction. Cholera microbes are hindered in their growth by the presence of even minute quantities of acid. Refined gelatin and isinglass that are used in making jellies and puddings, on the other hand, are alkaline, and hence, with the other constituents, make an alkaline and excellent food medium for the cholera microbe. Fortunately for us, by far the greater portion of our food has a faint acid reaction. The above-mentioned constituents of chocolate pudding are the only things commonly used by cooks that I can think of that have an alkaline reaction.

"Consequently this little research suggests an explanation of the excessive virulence shown by the cholera microbes in the chocolate pudding. The unfortunate partakers at the dinner party were swallowing cholera microbes that were actively reproducing, and that

were present in enormous quantities. The investigation also gives us a valuable hint as to how to avoid such accidents in future. In the present condition of cooks and cookhouses in India I believe it is almost impossible to prevent the microbes of enteric fever or cholera from being introduced occasionally. What I believe can be done is to avoid pampering these unwelcome visitors. Cold puddings made in the above-described way with gelatin or isinglass should obviously be avoided. In Indian cantonments, if cholera microbes are not about, the enteric microbe is usually not far off, and these cold puddings are as likely to be able to nourish one microbe as the other. Ordinary transparent jellies are probably less dangerous than opaque jellies, not because they are not capable of supporting the life of dangerous microbes, but because while being made they have to be boiled after the addition of white of egg, in order to clarify them. The boiling will destroy any cholera or enteric microbes present, and as these jellies are likely to be strained while hot, they are the less likely to be infected from the flannel bag or cook's loin-cloth that is used for the purpose."

This case shows well how roundabout may be the route by which the infection may travel, and the experiments made by Mr. Hankin also illustrate a fact which has already been mentioned, viz., that a very small quantity of the infection planted upon a suitable nutrient medium is capable of rapid self-multiplication to such an enormous extent as to become a poison of the greatest virulence if swallowed at the appropriate moment.

When, then, cholera is spoken of as a water-borne disease it must be remembered that that phrase is by no means meant to suggest that the microbe is always carried by water direct from the patient who gives rise to the infection to the one by whom the infection is received. There may be many stages in its progress from the one to the other, many generations of vibrios may intervene, and in the course of these generations the microbe may grow on many different sorts of material, but somewhere or other in its progress it will generally be found that water has had a hand in the distribution of the infection. Either water has itself been the medium in which it has grown, or has been the means by which it has been carried from place to place; the microbe sometimes being carried by sewage on to land used for the growth of vegetables which thus become infected; sometimes being washed into wells, or tanks, or streams, the water from which is used for cooking or for washing purposes and thus only indirectly gaining access to man; sometimes being carried directly into drinking-water and gaining immediate access to its next victim.

The phrase "water-borne" then, as applied to cholera, does not refer merely to the infection of great water supplies giving rise to vast epidemics, but has to do with cups and plates and cooking uten-

sils and the water in which they are washed; with salads and vegetables and the water with which they are irrigated in the garden and rinsed in the kitchen; and with the personal cleanliness of all who are concerned in the preparation, storing, and distribution of food or drink. In this sense nearly all cholera, at one part or another of its course from man to man, is water-borne.

It would be a matter of considerable interest to inquire what are the protective influences which communities weave around themselves so as to diminish the harmfulness of the diseases to which they are more especially exposed. It is too large a question to take up here, but it may be mentioned that, while in many places in India carelessness as to the water supply seems one of the predominating causes conducing to the continuous prevalence of cholera, there are also in many parts habits and traditional customs tending to preserve water, and especially well-water, from defilement. The caste system which is so all-pervading among the Hindus, and which in many ways opposes such obstacles to any advance or improvement in their condition, does to a not inconsiderable extent protect the wells; for while these are largely under the care of people of high caste whose occupations never lead them to foul their hands with fæcal matters, the people of low caste, who form the sweeper class, are never allowed to approach those wells which are used for the supply of drinking-water. Then the custom of eating their meals apart, and those customs of caste which divide even small communities into separate groups which hardly mingle for any purposes, tend much to stay the progress of infectious diseases.

During the great fairs and festivals, however, and in the course of the long pilgrimages which people undertake for the sake of attending them, such protective customs are of but small avail, and a study of the history of cholera, both in India and in the other countries to which it has been carried, shows how largely pilgrimages and wars, great gatherings and great movements of men, have conduced to the development of epidemics and to the spread of the disease over large areas. Nor is this surprising when it is remembered how even the most sanitarily disposed people have to put up with insanitary conditions whenever masses of men, unaccustomed to each other's ways, are crowded together, without any special provision for the disposal of their excreta, and are forced by the necessities of the case to make use of such water as may be found at hand.

In regard to the pilgrimages in and from India, however, there have always been special sources of danger, arising from the fact that the bathing in and the drinking of certain waters which are esteemed to be holy often form no small part of the festivals in question. The

mere aggregation of such crowds of people as attend some of these festivals, many of whom come out of districts in which cholera is almost always present, and are therefore almost certain to have among them some who are infected with the disease, would of itself be sufficient to scatter the malady far and wide; but the bathing gives additional opportunities for its diffusion. The town of Hardwár, at which every twelve years a great fair is held, has again and again been a centre for the diffusion of cholera. It is not within the area in which the disease is endemic, but the water of the Ganges at that spot, just as it escapes clear and cool from its upland home, has a peculiar fascination for the dwellers in the hot and vaporous plains, so that the Hardwár fair is always largely attended by pilgrims from the area where cholera is constantly endemic.

It has thus frequently happened that this great concourse has been followed by a wide diffusion of the disease outside its bounds. Besides the annual fair a Kumbh or great fair takes place every twelve years, and the occasion is looked upon by all Hindus as one of peculiar sanctity. Hence very large numbers avail themselves of the opportunity of bathing in the holy pool. In 1891, when the last Kumbh fair was held, 800,000 to 1,000,000 pilgrims assembled in the town, which has usually only 29,000 inhabitants. The risk run may be imagined. At these fairs the very aim and object of the pilgrimage is to bathe in the sacred river and to drink of its holy waters. Yet among the crowd, largely drawn as it is from the "endemic area," some one or other is sure to be affected with cholera and to foul the stream, giving to those who drink the fetid water in the hope of sanctity an infection which quickly brings about their death. The pilgrims, however, are not the only sufferers. Soon after the festival is over they are scattered to the four winds of heaven, carrying with them the infection. Some drag their weary bodies homewards till they drop by the wayside and die, others by boat or train are carried to distant parts, where, if they do not die *en route*, they set up fresh foci of disease from which infection spreads among their neighbors.

So much for the fairs of India. Clearly their danger, so far as the dissemination of cholera is concerned, depends largely on the fact that cholera is a water-borne disease.

There is, however, another pilgrimage, in this case a Mohammedan one, which involves even greater danger to the world outside, viz., the annual pilgrimage to Mecca; and the danger of this again is associated with the use of water in the ceremonial which is undergone by all the faithful on their arrival at the holy city. Every pilgrim drinks the water of the sacred well of Zem Zem. This is the well from which Hagar is said to have drawn water for her son Ishmael,

and the drinking of the water is a most holy rite. The supply, however, is not so large as might be desired for so great a crowd of pilgrims, and the manner of dealing with it at the well goes far to explain the heavy mortality which attends any outbreak of cholera among the Meccan pilgrims. At a given time they each in turn stand naked at the place appointed; a bucket of water is poured over each man; he drinks what he can of it, and the rest falls back into the holy well. Practically each pilgrim drinks of the washings of the rest, and when among the pilgrims there are persons suffering from cholera, there need be no surprise at finding that the disease spreads rapidly among them.

In 1866, within a few days of the ceremony, the road leading from Mecca was for twelve miles thickly strewn with dead bodies. Mecca thus, in cholera years, becomes a sort of cholera exchange, an emporium from which cholera is distributed to other portions of the world, and this danger is vastly aggravated by the greater rapidity of communication in these latter days.

When by weary marches, or sailing in small boats, months, nay sometimes years, were spent in the journey, those who were taken ill died in the transit; whole caravans melted away and ships with cholera-stricken crews were lost, together with their crowded cargo of holy pilgrims, and thus the outer world was saved. But with quicker means of communication, with railways and steamboats, pilgrims also have quickened their pace and have lengthened the stages of their journey, so that the infected ones have lived through hundreds instead of tens of miles before they dropped, and have thus surmounted the barrier of desert and sea by which Europe was formerly protected.

No longer does cholera pass round by way of Russia and the Caucasus, halting and starting afresh time after time. At one bound it is at Jiddah. Mecca becomes a centre of infection and Red Sea ports distribute the disease to Egypt and the south of Europe. In a double sense then is cholera a water-borne disease. By water the infection is carried to the mouth of its victim, and also by water is the victim carried long distances before he dies, so that the disease is able to traverse great seas which formerly were a barrier to its progress.

Malaria.

The question whether malaria should come within the category of water-borne diseases has been much disputed. The fact that in so many cases the infection is obviously carried by air rising as an emanation from the soil in malarious districts, and sometimes being car-

ried in the atmosphere for considerable distances, has tended to obscure the water-carriage of the disease. Nevertheless, its etiology, its association with a parasite which infests the blood corpuscles and seems to have as an ultimate host the female mosquito, an insect which is essentially a water insect, makes it extremely probable that water is largely engaged in its diffusion.

Malaria is generally looked upon as a disease of the soil. "The disease is particularly common in low, marshy regions which have an abundant vegetable growth. Estuaries, badly drained low-lying districts, the course of old river beds, tracts of land which are rich in vegetable matter, and particularly districts such as the Roman Campagna, which have been allowed to fall out of cultivation, are favorite localities for the development of the malarial poison. These conditions are most frequently found, of course, in tropical and subtropical regions, but it must not be overlooked that some of the most malarious districts of India are steep mountain slopes, and that many others both in India and elsewhere are equally free from moisture of the soil. Instances are common in which districts, previously healthy, have become temporarily or permanently malarious without apparent change in their physical conditions. The proof of the close relation between malaria and the soil is completed by the fact that malarious soil conveyed in boxes to healthy districts has given rise to outbreaks of the disease" (Notter and Firth).

Admitting, however, that the infection of malaria is soil-bred, the question is whether it enters man by way of the air he breathes or the water that he drinks. In regard to this there can be no doubt that it can enter in both ways.

It has long been the belief of those who dwell in marshy districts that marsh water can produce fever. Parkes found this belief current among the inhabitants of the highly malarious plains of Troy, the villagers saying that fever prevailed at all times of the year among those who drank marsh water, but only during the late summer and autumnal months among those who were careful to obtain pure water. "The same belief is prevalent in India. In the Wynaad district in Madras it is notorious that water produces fever and affections of the spleen. Instances are known where villages are placed under the same conditions as to marsh air, yet in some of them fevers are prevalent, in others not; the only difference being that the latter are supplied with pure water, the former with marsh or nullah water full of vegetable débris. In one village there were two sources of supply—a tank fed by surface and marsh water, and a spring; those only who drank the tank water got fever. In a village (Tulliwaree) no one used to escape the fever; a well was dug, and fever disappeared, and,

during fourteen years, had not returned. Another village (Tambatz) was also 'notoriously unhealthy'; here also a well was dug, and the inhabitants became healthy. Nothing can well be stronger than the positive and negative evidence here given. Moore also noted his opinion of malarious disease being thus produced; and Commaille has since stated that in Marseilles paroxysmal fevers, formerly unknown, have made their appearance since the supply to the city has been taken from the canal of Marseilles. . . . The Upper Godavery tract is said to be the most aguish in the province, yet there is not an acre of marshy ground; the people use the water of the Godavery, which drains more dense forest land than any river in India" (Notter and Firth).

Cases have also been recorded in which malaria has appeared on ships at sea which have obtained water from marshy and malarious sources. Boudin gives the following: "One hundred and twenty soldiers embarked in the transport *Argo* at Bona in Algeria for Marseilles. During the voyage 111 of them, 13 of whom died, suffered from different forms of malarial fever. Two other vessels, carrying between them 680 soldiers, also from Bona, and arriving at Marseilles the same day as the *Argo*, had no cases of illness at all, and the only ascertainable difference of circumstances between the troops in these ships and those in the *Argo* was the difference of drinking-water. The latter were exceptionally supplied with water, which was said to have an unpleasant smell and taste, from a marsh near Bona; those on the other ships were supplied with good water. Finally, the nine soldiers on the *Argo* who escaped were said to have purchased wholesome water from the crew of that vessel."

Hirsch, however, considers that there is no proof of the propagation of the disease by means of drinking-water, and he thinks that the cases which have been brought forward to prove it do not bear the construction put upon them.

W. North also points to the fact that "the healthiest parts of the city of Rome are supplied by water admitted to be the best in the world, and which rises—to take the Acqua di Trevi or Acqua Vergine as an example—on unenclosed land, in springs which bubble up and cover the surface in a locality so unhealthy that to pass several nights there in August might involve risk to life, certainly to health."

It is also a matter of some importance to observe that notwithstanding the great improvements which have taken place in the character of the water supplied to the seamen in our royal navy, and especially the large use of distilled water, no diminution in the proportion of cases of malarial fevers seems to have taken place.

The discovery of the malarial parasite, however, and the many

facts which have been observed in regard to its life history, all point to the conclusion that at least one of the ways by which the infection of malaria may be introduced is by means of water; not that it by any means follows that water is the only route by which it gains access to man.

Dr. Patrick Manson, who has devoted a great deal of attention to the subject, believes that, as is the case with so many other parasites, that of malaria dwells in different hosts, and that the alternation lies between man and the mosquito.

Even more than in the case of the filaria the only way by which the parasite can escape from man's body is in the blood, for the malaria plasmodium has its home actually within the red corpuscles, and there is every reason for believing that the agency by which it is removed out of the human body is the proboscis of the mosquito, which creature forms its other host.

The history of the parasite within the blood of man has been fairly worked out so far as concerns the more ordinary benign tertian forms of ague.

The occurrence of the rigor is associated with the sporing stage of the parasite, which becomes segmented, escapes from the corpuscle in which it had been lying, and breaks up into spores. These attach themselves to and enter other blood corpuscles, in which they go through various phases of development, till at the proper period they in turn form spores again, and the whole process is repeated. "Although we cannot directly watch the evolution of any individual parasite, we are driven to the conclusion that one form passes into the other in a very definite way, that we are contemplating the birth, growth, and multiplication of an organized being, conducted on a regular and definite plan. We conclude that the large pigmented intracorpuscular body is the mature animal prepared for sporulation, that the morula-like mass is the same with the sporules formed, and that the spherules into which it breaks up on its leaving the blood corpuscle are spores. These spores on becoming free attach themselves to the red blood corpuscles and begin to grow at the expense of the hæmoglobin, which they convert into their proper tissue and into the black pigment, which must be regarded as a sort of excrementitious product of the parasite's digestion. In about forty-eight hours they have attained their maximum growth and prepare for sporulation, the nucleus and nucleolus becoming diffused through the protoplasm. Presently the nucleolar matter collects at a number of points and around these points the protoplasm arranges itself in the little spherules, forming the elements of the morula mass, each little spherule or spore being the rudiment of the new being into

which it may develop on the bursting up of the morula mass at the termination of the cycle" (Manson).

Outside the body, however, quite a new form of development takes place, and, instead of repeating again the same cycle, flagellate spores are formed.

Two questions then arise: How does the parasite pass from one man to another? and what is the reason for the development of these flagellate spores so soon as the organism is removed from its former environment within the blood-vessels?

The answer to these questions is, according to Dr. Manson, to be found in the fact that the alternate host of the parasite is the mosquito. Soon after the blood is drawn by the mosquito the parasites contained in the corpuscles, if they are in the proper stage, the so-called crescent stage, rapidly undergo change, become spherical, and throw out flagellate spores which, by aid of their power of active movement, work their way out of the stomach of the mosquito and find for themselves a home in the tissues of that insect, where again they lie dormant until its death. To understand what may happen to them then it is necessary to consider a little chapter in the life history of the mosquito.

"The female mosquito after she has filled herself with blood—the male insect is not a blood-sucker—seeks out some dark and sheltered spot near stagnant water. At the end of about six days she quits her shelter and alighting on the surface of the water deposits her eggs thereon. She then dies, and, as a rule, falls into the water alongside her eggs. The eggs float about for a time, and then in due course each gives birth to a tiny swimming larva. These larvæ, in virtue of a voracious appetite, grow apace, casting their skins several times to admit of growth. Later they pass into the nympha stage, during which time they float on the surface of the water. Finally, the shell of the nympha cracks along its dorsal surface and a young mosquito emerges. Standing, as on a raft, on the empty pelt, the young mosquito floats on the surface of the water while its wings are drying and acquiring rigidity. When this is complete it flies away. The young mosquito larvæ, to satisfy their prodigious appetites, devour everything eatable they come across; and one of the first things they eat, if they get the chance, is the dead body of their parent, now soft and sodden from decomposition and long immersion. They even devour their own cast-off skins. In examining mosquito larvæ one often comes across specimens whose alimentary canals are stuffed with the scales, fragments of limbs, and other remains of the parental insect and larval pelts" (Manson).

It is clear that in consequence of this habit of devouring the in-

fected bodies of their parents the young may become infected, and thus the plasmodium disease may pass from generation to generation of mosquito independently of the presence of man, may spread from pool to pool, and become scattered broadcast about the country, infecting the water wherever mosquitos dwell, and thus gaining access to the body of man when he drinks the infected fluid.

It is clear also that the parasite undergoes multiplication within the blood of man, generation after generation of spores being cast out into the blood stream and finding a nidus for further development within fresh red corpuscles.

It thus appears that although both man and mosquito become the hosts of the malaria parasite, they are not both necessary to complete the life cycle of the individual, for many generations may be passed in each condition. Whether, however, the parasite can continue to live indefinitely without transference from one host to the other is a point on which at present we have no real knowledge. Probably sooner or later such transference must take place.

The intracorpuscular phase is so peculiar and so specialized that it is impossible to look upon it otherwise than as a normal part of the life cycle of the parasite, and it is difficult to avoid the conclusion that the plasmodium is primarily a parasite of the blood cell, whether of man or of other animals, and that the cycle of its life (including in that term many generations) lies between the mosquito and blood of those animals on which she naturally feeds; the phases taking place alternately, within the corpuscle; within the stomach of the mosquito; within its tissues; then in water; and, when swallowed by an animal, within that animal's stomach; and then, after boring through its tissues, within the corpuscle again. When then man intrudes into a malarious district he may breathe air charged with germs of the disease arising from the soil, to which it has been carried by the mosquito, or he may drink water infected in the same way. He may thus become attacked by malaria, may become charged with the malarial parasite, and may in turn infect those mosquitos which may bite him; the man taking the place of some animal as yet unknown as the host of the plasmodium. If such views are to be accepted as correct, there can be no doubt as to the propriety of classing malaria among the water-borne diseases. At the same time it must be admitted that, as usually met with, malaria is an air-borne disease so far as concerns the final stage of the introduction of the infection into man; and that what we now know of the behavior of typhoid infection in the presence of malaria throws considerable doubt upon the purely malarial nature of some of the cases relied on by those who believe the latter disease to be water-borne.

Dysentery, Diarrhœa, and Yellow Fever.

Certain diseases have now to be considered in regard to which, however confident one may feel that in certain cases they are distributed by means of water, the proof of such a method of conveyance is difficult to obtain. In this category may be placed yellow fever, dysentery, and many forms of diarrhœa. These diseases are not generally looked upon as directly infectious from man to man, yet they are apt to occur in epidemics under such circumstances as to make it evident that the discharges from those who suffer from them do play some part in their propagation. They are, in fact, infective diseases the specific virus of which passes some portion of its life outside the body; and, although the exact route by which, in the case of most of them, the infection enters man is as yet unknown, it seems almost certain that one way at least is by drinking water.

The word dysentery is often used in a somewhat vague way to describe various ailments which are characterized by the occurrence of frequent stools with straining, griping, and discharge of blood and mucus. It occurs in many forms, some of which, no doubt, are but aggravated cases of inflammatory diarrhœa, caused perhaps by drinking water containing decomposing organic matter. Real tropical dysentery, however, is a specific disease, arising from infection by a specific organism, and is undoubtedly water-borne.

The *amœba coli*, as it is described by some, or the *amœba dysenteriæ*, as it is called by others, is found not only in the stools and the intestines, but also in the abscesses which are such frequent sequelæ of this disease.

In many hot countries dysentery is more or less endemic, both sporadic cases and epidemics occurring at all times of the year, but most frequently in the summer and the autumn. In more temperate climates, although sporadic cases are met with in the hot months, it is chiefly known as an epidemic disease occurring in connection with overcrowding, insanitation, and impure water.

When many people are crowded together under conditions of imperfect sanitation, whether in the tropics or in temperate climates, the disease is very apt to take on the epidemic form, and thus it has many times happened that dysentery has been more fatal to armies in the field than all the battles put together.

Dysentery is not directly contagious from person to person. Nevertheless, it is a definitely infective disease, the infection lying in the discharges and gaining access to man by reason of the soil or the drinking-water becoming polluted. It may thus be looked upon as analogous in its mode of distribution to cholera or typhoid fever.

In the preventive treatment of dysentery, as indeed of cholera and other diseases of the same type, it is important not to confine the attention solely to the means of securing from infection that prime commodity—water.

The predisposing causes of the disease must be considered besides the actual infection by which it is set up, and among these must be noted all causes of indigestion, and of what would in ordinary times and seasons be spoken of as diarrhœa: the eating of unripe or overripe fruit; the drinking of spirits, especially in view of the fact that this practice usually involves also the drinking of more or less impure water; excessive exertion; and exposure to chills. All these have the effect of inducing a condition of the intestine which, without having any direct connection with the infection, leaves them open to its attacks. If one would prevent the disease such predisposing causes must be most carefully guarded against. The direct cause of the malady, however, is infection by a living germ which is somehow or other carried from a preceding case, and this germ, although gaining access in various ways, is no doubt usually carried by water.

Under the heading Diarrhœa are classed a number of conditions about the nature and causes of which we possess very little exact knowledge. Very often these are, no doubt, mere cases of poisoning by toxic products arising either from the drinking-water or the soil from which it flows being charged with decomposing matter.

It is quite possible that in some cases diarrhœa may be the result of an actual infection by living micro-organisms, but even where this is the case the disease is not passed directly from patient to patient. It returns again to the soil, and only as the combined result of insanitary conditions and of such surroundings, as to moisture and temperature, as are suited to the growth of its virus can the disease become epidemic. As an instance of this we may take ordinary summer diarrhœa, which in certain parts of England carries off many children every year. Whatever the micro-organism involved in the causation of this disease, it has been shown by the late Dr. Ballard that prolonged heat, a heat that shall penetrate far into the soil, is necessary for the production of its evil consequences.

What is the exact mode by which the infection is introduced into the human body is as yet unknown, but it is difficult not to believe that water is largely involved, although it may not be the only means by which it is conveyed.

Yellow fever is an acute febrile disease of tropical and sub-tropical countries. Its distribution as an endemic malady is peculiarly limited. Its infection can be carried long distances, and is quite capable

of taking root in unaccustomed soil so long as a suitable temperature, which must not be less than 70° F., is maintained, but not otherwise. It is always most fatal in the warm season, and it is stated that the occurrence of a sufficiently low temperature to freeze the ground at once puts a stop to an outbreak of the disease. Its epidemic prevalence depends greatly upon the existence of insanitary conditions, it occurs almost exclusively in the crowded parts of towns, and especially of those having a maritime trade, and not only does the infection seem to cling to clothing but also attaches itself with great tenacity to ships. In view, then, of the fact that the spread of this disease is so peculiarly limited by external conditions, we may feel certain that some intermediate, external, saprophytic stage of existence is essential to the due propagation of its virus, and, as is the case with all diseases the infective germs of which grow outside the body, that water is one at least of the vehicles by which they gain access to the patient.

In regard to yellow fever, as also in regard to dysentery and the various forms of diarrhœa which may be looked upon as specific, this point is to be noted—that each seems to prevail most amid certain external surroundings, and that so far as these diseases are infectious from man to man these external conditions are of more importance than direct transmission of the virus from patient to patient. It is also well to note that the prevalence of each and all of them seems to be specially linked with the existence of general insanitation, in which term is included laxity in the means taken to protect water supplies from pollution, and that, although in diarrhœa and yellow fever we have not the same proof of water carriage that we have in reference to dysentery, there can be but little doubt that in many instances they are all water-borne diseases.

PREVENTIVE MEASURES.

The prevention of water-borne disease is to a large extent a matter for the engineer. It may be well, however, to emphasize a few biological points which have come to the front during recent years, points which must be reckoned with by those who are engaged in the provision of safe drinking-water.

It will have been seen from the whole tenor of what we have written how thoroughly we look upon the subject of water-borne disease as a problem in biology, and we would wish to emphasize in the strongest way that what is wanted in a healthy water supply is not a chemically pure water, nor a bacteriologically sterile water, but a water such as the human race has used during its long period of

evolution, and one free from those pathogenic organisms which prey upon man, and, by the diseases they produce in him, tend to check his further progress.

The great mass of the diseases which are water-borne depend on the presence of living disease germs in the water, and it is a simple and easy suggestion to kill all such germs by heat. We have advocated what we have called the "policy of the tea-kettle," and we hold that in the presence of an infected water supply sterilization by boiling is the most effectual domestic means at our disposal for protection against disease. But in regard to all processes for the production of sterile water, water which is devoid not only of pathogenic organisms but of organisms of all sorts, it must be remembered that such a fluid is often extremely well fitted for the growth of disease germs, and that if exposed to infection pathogenic organisms will often develop in it far more readily than in water which contains its due supply of those "water organisms" which seem to be the natural provision for maintaining the purity of water. The result is that in all cases in which the processes used for the purification of water end in the production of a sterile water, the greatest care must be taken to protect it from further contamination before it is used. In the case of public water supplies the engineering and administrative details of which are properly carried out, especially where the source of the supply is far removed from chances of infection and the water after leaving the filter beds is protected by being distributed under pressure, safety is generally secured. Where, however, an attempt is made to purify water by heat on the large scale—where water is boiled in large quantity, and has to be cooled while surrounded with possible sources of infection, it is often very difficult to protect the boiled water from pollution. Its natural protection is removed, and if dealt with in bulk the water must remain for a considerable time, during the process of cooling, at a temperature peculiarly fitted for the growth of pathogenic organisms should they gain access to it. The result is that while our recommendation of the tea-kettle remains good, and probably always will remain good, as a means of purifying water on the small scale, it must not be argued therefrom that the sterilization of water on the large scale by great boilers, or even by distillation, will always be equally successful unless very constant care be taken to protect the product during the time of cooling and of storage.

The purification of water on the large scale is usually effected by means of sedimentation, filtration, and, in the case of some hard waters, by various modifications of Clark's lime process for removing temporary hardness.

Sedimentation in tanks is probably almost exclusively mechanical or physical in its mode of action; but the gradual purification which takes place in a flowing stream so far as pathogenic micro-organisms are concerned, although partly the result of sedimentation, is no doubt also to a large extent the outcome of the action of those water organisms which, whether or not it be from a "struggle for existence," do, as a fact, ultimately develop in flowing water to the exclusion of exotic pathogenic bacteria.

Many most interesting investigations on this subject have been made by Dr. Percy F. Frankland. Among other things he has ascertained that so far from it being possible to lay down any rule as to the number of bacteria which are permissible in a potable water, it may sometimes occur that there is safety in the presence of a large number of them. He introduced typhoid bacilli into deep well water, which was almost wholly free from bacteria, into Thames water which contained a large number, and into Loch Katrine water in which the number was intermediate between the two; and as a result he found that the typhoid bacilli died off more rapidly in the Thames than in the Loch Katrine water, while they persisted longest in the sparsely populated deep well water. Thus the longevity of these pathogenic bacteria was inversely proportional to the bacterial population of the waters into which they were introduced.

Filtration used to be looked upon as a merely mechanical process. Then, when it was observed how different was the chemical composition of the effluent compared with the unfiltered water, and how largely the nitrogenous constituents of the water became oxidized in the process, it was thought that the activity of the filtering medium was due to some power possessed by it of condensing oxygen in its pores and thus presenting it in an easily assimilable form to the oxidizable material contained in the water. Some years ago, however, it was shown by Professor Koch that the efficacy of a sand filter depended more upon the layer of slime which formed on the surface than on any action within the layer of sand itself, and it is now generally recognized that the efficiency of a sand filter depends to a large extent on the presence of its layer of bacterial slime and upon the care which is taken to preserve its continuity unbroken. Recent observations, however, have tended to show that even the deeper portions of a sand filter possess considerable power in the purification of water, and everything goes to show that the more nearly we approach to those natural processes by which spring water obtains its purity the better results do we obtain.

The filtering area should be large and its surface should be covered by living vegetable matter which should not be disturbed;

and after permeating this layer the water should undergo a slow process of filtration through a very considerable thickness of filtering medium. If it is once recognized that the process is a vital one, and that in its course a process analogous to fermentation has to take place, by which decomposable material becomes oxidized, the necessity for slowness of filtration becomes apparent; and when it is seen that the removal of pathogenic and other organisms is not a matter of mere mechanical separation, but of their substitution and destruction, one may almost say their digestion, by those organisms which exist in and upon the surface of the filter, it becomes obvious how necessary it is that the area used shall be large and the thickness of the bed considerable.

As is well known, the temporary hardness of water, which is due to calcium carbonate being dissolved in an excess of carbon dioxide, can be removed by adding to the water such an amount of calcium hydrate as will combine with the free carbon dioxide, the result being that all the lime salt, being deprived of its solvent, falls to the bottom of the tank as a fine white sediment. It has been found that this process, besides removing the temporary hardness of the water, helps also to a remarkable degree in removing the suspended matter, including the bacteria, which may be present in it at the time. It does not appear likely that any such process as this could ever be trusted to render an impure water fit to drink, but its adoption where it is available certainly very much lessens the work thrown upon the filters. It is in fact a sort of assisted sedimentation, the heavier particles of lime carrying down with them the lighter particles of protoplasm.

There can be no doubt that every community should endeavor to get its drinking-water from the purest source available. Human appliances are fallible, and even at the best are apt to break down from unforeseen and often unpreventable causes; hence, wherever it is possible, it is worth while to go to much trouble to obtain so important an article as pure water from an unpolluted gathering ground. This, however, is not always possible, and in such case, where, as a *dernier ressort*, people are driven to the use of water which has been exposed to chances of infection, they may at least have the satisfaction of knowing that good potable water can be manufactured for their use by the aid of sedimentation and sand-filtration. It must never be forgotten, however, that this is a process which requires a large outlay both in works and in management—a far larger outlay than many will admit. The safety of the process depends not only on having a very considerable filtering area, and upon this being so arranged that any section can be used quite independently of the

rest, but upon such a careful and constant bacteriological inspection of the filters as shall insure their continuous efficiency; all of which costs money. Pure water, however, is worth much, and communities may consider themselves well repaid for their outlay if they find themselves thereby protected from attacks by water-borne diseases.

CONCLUSIONS.

To sum up then our present knowledge on the subject of water-borne disease, it may be said that:

1. Entirely irrespective of any infection by "disease germs" water containing decomposable material, or flowing off land containing organic matter in a state of change, may produce disease—commonly in the form of diarrhœa.

2. Such water, however, may also produce disease, in a secondary manner, by the products of decomposition, although harmless themselves, rendering other poisonous substances soluble, as in the case of peaty water dissolving lead.

3. Water may be necessary for the due accomplishment of certain acts or phases in the life history of certain parasites, as, for example, the sporing stage of certain entozoa, and the cyclops stage of the filaria. In some of these cases water may also form the vehicle by which the parasite is carried back to man; but in others, essential as water may be to one or other stage in the life cycle of the parasite, it may not be the means by which this is finally brought back again to its new host.

4. Water may be necessary for the saprophytic stage of growth undergone by certain pathogenic micro-organisms outside the human body, as, for example, in the case of cholera, typhoid fever, and many forms of dysentery and diarrhœa, and for the alternate phases of such pathogenic organisms as the malaria parasite, which probably is but a type of many forms as yet undiscovered.

5. Water may not only be the medium in which the pathogenic organisms grow, but may be the vehicle by which they are distributed. Of this typhoid fever and cholera are the standing examples, and in regard to these it may be said that every step has been traced out; but there can be little doubt that in the distribution of many other diseases water plays a more or less prominent part, sometimes carrying the infection direct to the drinker, sometimes transporting it from the invalid to places fitted for its external growth, and in very many cases serving as the actual material in which such growth takes place.

Bibliography.

Garrett, J. H. : Action of Lead on Water, 1891.

Notter and Firth . The Theory and Practice of Hygiene, 1896.

Sternberg, G. M. A Manual of Bacteriology, 1896.

Abbott, A. C. : Principles of Bacteriology, 1896.

Allbutt, T. Clifford : A System of Medicine, 1896.

Davidson, A. : Geographical Pathology, 1892.

——— Hygiene and Diseases of Warm Climates, 1893.

Macnamara, C. : Treatise on Asiatic Cholera, 1870.

——— A History of Asiatic Cholera, 1876, and the same brought up to date 1892.

Hirsch, August : Handbook of Geographical and Historical Pathology, Translated by Charles Creighton, 1883.

Frankland, Percy : Micro-organisms in Water, 1894, and other papers.

Annual Reports of the Medical Officer of Health of the Administration County of London, 1894.

Report of the Royal Commission on Metropolitan Water Supply, 1892–93.

Memorandum and Reports to the London County Council on the Report of the Royal Commission on Metropolitan Water Supply, by the Medical Officer of Health and others, 1894.

Report by the Chemist to the London County Council (W. J. Dibdin) on Experiments on the Filtration of Sewage Effluent, 1895.

Hart, Ernest: Cholera, An Address Delivered before the American Medical Association, 1893.

——— The Nurseries of Cholera, 1894.

——— Water-borne Typhoid. British Medical Journal, 1895.

Snow, John : On the Mode of Communication of Cholera, 1849.

Report on Cholera in Europe by the Medical Officer to the Local Government Board, 1894. To which is appended a translation of Professor Koch's paper on "Wasserfiltration und Cholera."

Manson, Patrick: Benign and Pernicious Malarial Fevers. British Medical Journal, 1896. Gulstonian Lectures on the Life History of the Malaria Germ Outside the Human Body, 1896. Reported in the British Medical Journal.

Report to the London County Council on the Analytical Investigation of London Water Supply, 1896.

Reports to the London County Council on Sewer Air, by J. Perry Laws, 1892.

Report to the London County Council on the Micro-organisms of Sewage, by J. Perry Laws and F. W. Andrewes, 1894.

Report of the Medical Officer to the Local Government Board on Oyster Culture in Relation to Disease, 1896.

Wood, G. E. Cartwright: Report to British Medical Journal on the Circumstances under which Infectious Diseases may be conveyed by Shell-Fish, with Special Reference to Oysters.

Seventeenth Annual Report of the State Board of Health of the State of Connecticut, containing Report on an Outbreak of Typhoid Fever at Wesleyan University, by H. W. Conn, 1894.

Annual Reports of the Medical Officer to the Privy Council, 1858 to 1870, continued as

Annual Reports of the Medical Officer of the Local Government Board to 1894, containing Reports of Inquiries into Outbreaks of Infectious Diseases.

THE DURATION OF THE PERIODS OF INCUBATION AND INFECTIOUSNESS IN ACUTE SPECIFIC DISEASES.

BY

DAWSON WILLIAMS,

LONDON.

INCUBATION AND INFECTIOUSNESS IN ACUTE SPECIFIC DISEASES.

INCUBATION period is the term applied to the time which elapses between the establishment of a *contagium vivum* in the body and the onset of the characteristic symptoms. The term is, of course, older than bacteriology, for the germ theory of disease, which assumed that the introduction of a minute quantity of the living infective agent into the body was followed by its multiplication in the blood or in the tissues, led necessarily to the presumption that a certain period of time must pass during which the living infective agent, though multiplying in the body, was not yet present in numbers sufficient to produce obvious symptoms. It might have been supposed, however, that this period would not have had a well-defined termination, but that the transition from apparent health to the developed disease would be gradual, and would correspond to a gradual increase in the numbers of the living infective agent.

Still confining our attention to a theoretical consideration of the multiplication of the infective agent, it will become apparent that though it might be expected that the development of symptoms would be gradual, yet as time went on the severity of the symptoms would, it might be anticipated, increase with progressive rapidity. Suppose, for the sake of argument, that n microbes were introduced into the body, and that each was capable of dividing into two thrice in twenty-four hours, and that none were destroyed, then at the end of the third day there would be $n \times 500$ microbes present, but at the end of the fourth day there would be $n \times 4{,}000$. It might very well be that the symptoms produced by $n \times 500$ microbes would be so slight as to escape observation, whereas those produced by $n \times 4{,}000$ would be very well marked. The disease would then seem to come on suddenly during the fourth day. Max Neisser[1] has recently made some calculations as to the rate of the multiplication of the diphtheria bacilli which are interesting in this connection. He found that one million and a half of these microbes inoculated into serum became in the course of six hours sixty millions, in nine hours five hundred millions, and in twenty-four hours eleven hundred millions. The rate of increase between six and nine hours was thus extraordinarily rapid.

In broth the multiplication was much less rapid—one million and a half became one hundred and twenty millions in twenty-four hours. It is not, of course, for a moment suggested that Neisser's experiments represent the rate of growth on the surface of mucous membrane, but they illustrate the fact that it increases with a rapidity which is progressive, although the progression is not mathematically regular. Still it throws light on the processes which are taking place during the period of incubation, in the case of certain infections at least, though the course of events is more or less profoundly influenced by other factors to be considered immediately. A case of diphtheria of the skin recorded by Max Flesch[2] is of great interest from this as well as from some other points of view. There is good reason to believe that the infection was carried to the spot which afterward became the seat of the diphtherial membrane, on August 10th at 11 A.M. No sign of any membrane was observed fifty-six hours later, but the next morning there was a well-marked patch of membrane.

G. H——, a girl, aged 2½ years, was scalded over the right side of the face and the front of the neck and trunk, on August 3d, 1895. The scald was more severe over the chest and abdomen than over the neck and face. The child came under treatment one and one-half hours after the accident, and before any domestic remedies had been applied. The scalded surface was treated with Lassar's salicyl vaseline (two per cent.), and covered with cottonwool retained by a bandage. The dressing was renewed daily. On the second and third days there was slight fever, the highest temperature being 39.6° C. (103° F.) on the third day. Fever then disappeared and the child felt well. On August 10th the superficial scald of the face and neck was covered with young epidermis, and the dressings were not reapplied to this part; whereupon the mother exclaimed, "I must kiss her sweet little neck," and before Flesch—who, as he says, objected on principle, and not because he had any thought of infection—could interfere, she did so. On the following day, August 11th, in the morning, the mother complained of sore throat, and was found to have angina of both sides, with a small deposit on the left tonsil, apparently follicular angina. She was told to keep away from the child, and in the evening the deposit on the tonsil had enlarged, so that the diagnosis of diphtheria became probable. This suspicion was confirmed on August 12th, when the mother's sister, who had taken charge of the child, began to suffer from a similar affection of the throat. The father also had a sore throat, but without membrane. The mother had a severe attack, and the disease was typical also in her sister. Both women were treated by injections of antitoxic serum; both had hemorrhagic nephritis, but both recovered. The father subsequently had a small patch on the left tonsil. The child had no affection of the throat, but on August 13th, when brought to be dressed in the morning, a very notable change was observed in the part of the original scald which had been healed on

August 10th. Over an area about one inch and a half in diameter on the neck, just above the right clavicle, the skin was white and swollen; around this area the skin was œdematous, and the œdema spread so rapidly that by the evening the right eye was closed. The white area was sharply circumscribed. Remembering the history of the kiss, Flesch was disposed to make the diagnosis of diphtheria of the skin; and Dr. Benario, on making bacteriological cultivations, obtained on agar culture medium "typical, very strongly growing colonies of the diphtheria bacillus." The child was treated with the antitoxic serum, of which it received two injections, and the salicin vaseline was reapplied. By August 16th the œdema had disappeared and the white patch was replaced by a granulating surface. The general condition of the child was good, and the throat remained quite unaffected. Some time later, however, it suffered from a slight but distinct and characteristic paralysis of the palate. There was not at any time any fever or alteration in the frequency of the pulse. The urine could not be obtained for examination. Fever, Flesch observes, is sometimes absent even in diphtheria of the throat. How the mother contracted diphtheria was doubtful. The house was well built and the rooms were well ventilated, but the mother in her attendance on the child during the night was exposed to chills, which may have predisposed her to contract diphtheria on a slight exposure. It was remarkable that the diphtherial process in the child was limited to the part of the scalded surface which had become covered with new epithelium and did not extend to the granulating surface below, which was covered with serous discharge. The diphtherial process began apparently at or near the spot kissed, and was limited to its neighborhood.

In this case the infection by the kiss took place about 11 A.M. on August 10th, and the diphtheria must have commenced between 7 P.M. on August 12th and the morning of August 13th; that is to say, fifty-six to seventy-two hours after infection.

The general symptoms of diphtheria are due not to the presence of the bacilli in the tissues—for, at first and in the main throughout, they are confined to the site of the local lesion—but to the circulation of soluble toxins or of the products of their action on the fluids and tissues of the body.[3] It may safely be assumed that the amount of poisonous material is at first small, and that it is constantly being eliminated or destroyed. It is only when the amount of poisonous matter in circulation has risen above a certain proportion that it could be expected to produce symptoms. Analogous considerations apply *mutatis mutandis* to the majority of acute infectious diseases.

Further, after the infectious process has reached a certain stage of development, after it has produced fever or other pronounced symptoms, not only is production increased, but destruction and elimination are diminished, and there is therefore an actual accumulation of toxic substances in the body. Again, not only does the production

of toxic substances take place with progressive rapidity, but in severe disorders the rate of destruction and elimination of these bodies probably diminishes with even greater rapidity, for one of the earliest results of infectious fevers is a profound degenerative change in the protoplasm of the emunctories, especially the kidneys and liver. This must interfere with the elimination of effete and toxic materials. The toxicity of the urine is diminished very remarkably during the febrile stage of some at least of the acute infectious diseases. Roger and Gaume[4] have found that a patient suffering from acute pneumonia eliminates only one-half or one-third as much toxic matter by the urine as in health, and that the crisis is attended by a large excretion of such toxic matters. Roque and Lemoine[5] observed a very similar event in malarial fever; the toxicity of the urine was five times as great immediately after a febrile paroxysm as it was before. When quinine was given the toxicity became still greater. In typhoid fever again defervescence is often attended or preceded by the passage of a large quantity of urine containing a high proportion of "extractives" and of total solids. Considerations of this nature lead also to the expectation that the onset of the general symptoms of an acute infectious disease would not be by a regular and slow increase from the time of infection, but rather in an explosive manner.

So far the tissues have been regarded as though they offered a passive field for the growth of the microbe—such a field as is afforded by a flask of bouillon or a tube of nutrient gelatin or serum. This, however, is very far from being the case. The presence of a pathogenic microbe leads as a rule immediately to the phenomena of phagocytosis, and it is only when the dose of toxin produced overpasses a certain limit that the phagocytes draw off and leave the field free to the microbe for its multiplication. Moreover, from an early stage of certain acute infectious diseases, and probably of all, the production of toxins is attended by the appearance of antitoxins which oppose and in time neutralize the deleterious action of the toxins. For the present argument, however, the most important point is that phagocytosis tends for a time to check the multiplication of the microbe, and that this tissue resistance may after a time become almost suddenly ineffectual or inoperative, thus leaving the microbe free to multiply with the greatest rapidity.

It has often been maintained that the incubation period of many diseases may be influenced greatly by the "dose" of the infection received. This view has been asserted in particular with regard to typhoid fever. In certain epidemics in which milk was the vehicle by which the infection was distributed, it has been observed that those first attacked were persons who had consumed the milk in large

quantities and with regularity, while those last attacked were persons who had taken the milk in small quantities and on only one or few occasions. Ballard,[6] in one epidemic investigated by him for the Medical Department of the Local Government Board (England), obtained particulars of 43 cases. It was specially mentioned that 19 of these persons used the suspected milk freely as an article of diet. All but 4 of these 19 applied for medical aid within the first fortnight of the outbreak. By 24 of the persons attacked very little milk was taken, and of these 17 sought medical aid in the third and fourth weeks of the outbreak, and 3 only in the first, and 5 in the second weeks of the outbreak. W. H. Power,[6] in an epidemic due to infected water, found some reason to think that the incubation period might have been shortened in some instances. On the other hand, the same careful observer records a case in which typhoid fever followed a single draught of infected milk at an interval of three weeks, whereas during the same outbreak "great 'milk-drinkers' were proportionately early sufferers." In cases in which the period of incubation is greatly prolonged beyond the ordinary, of which event typhoid fever again presents perhaps the best authenticated examples, it may be questioned whether we have not in reality to do with a condition of latency preceding the true period of incubation. Chantemesse, indeed, asserts that "certain individuals retain for a long time in their intestines, and perhaps even in the substance of their tissues, typhoid germs which develop ill until the occurrence of some favoring circumstance." A similar retention of the infective agent in a condition of quiescence or latency takes place probably not very infrequently in diphtheria, and the microorganisms of pneumonia and of suppurative diseases may be present in the cavities or on the surface of the body for long periods, without exciting any pathogenic effect until some deterioration of the general health or of the power of local resistance enables them to become established, to multiply, and to produce their characteristic pathological consequences. (An interesting collection of observations bearing on this and cognate points will be found in a paper read by Washbourn before the Royal Medical and Chirurgical Society of London.[7]) So far as concerns the acute specific diseases, occurrences of this nature must be very exceptional; at least the evidence of such occurrences is very scanty. With regard to some, indeed, the evidence is all the other way, and in favor of the opinion that an infective agent once established in the body either produces the disease within a period more or less precisely limited or is destroyed.

When due weight is allowed to the variety of circumstances which must be assumed to have an influence on the duration of the period

of incubation, it must be felt that the wonder is not that the period varies for the same disease in different individuals, but that in many diseases, of which smallpox affords the most striking example, it is so nearly constant as it is. The duration of the period is, in fact, a part of the natural history of each acute specific disease, and an acquaintance with its nature and variations is of considerable importance in practical medicine. Coupled with a knowledge of the duration of infection in affected individuals, it forms a large part of the foundation upon which rest modern methods of preventing the dissemination of acute specific diseases.

The incubation period determines the length of time for which a susceptible individual who has been exposed to infection should be kept under observation, before it can be said that he has escaped. It is of assistance often in diagnosis, if a history of exposure to infection can be obtained. An acquaintance with the duration of infection and with the period of disease at which it commences or is most intense, will often serve to guide the practitioner under difficult circumstances as to the precautionary measures which it may be worth while to take to guard other members of a family or school from the infection.

In estimating the period of incubation of any disease, the most trustworthy evidence is afforded by cases in which the symptoms have begun at a known date after a single exposure to infection. Cases in which the exposure has begun at a known date and continued thereafter are of value in determining the shortest period of incubation, and cases in which exposure after lasting for some time has ceased at a known date serve to help in fixing the maximum period of incubation. It is desirable that these restrictions should be borne in mind, as statements are frequently made on facts which do not really bear on the point to be determined—as when, for example, long periods of incubation are asserted on the strength of the fact that a person has been exposed to infection for, say, a month before developing the disease. In such cases the disease has, it is fair to assume, only commenced to become established in the body at some period after the beginning of exposure, owing to some circumstance connected with the health of the individual himself, to social or other conditions which have brought him into more intimate relation with the person suffering from the disease, to the fact that the disease is one in which infection is more easily disseminated at a late period of its course or during convalescence, or because exposure to fomites has occurred only when convalescence has advanced far enough to permit the invalid to resume his ordinary wearing apparel used during the early stage of his illness.

Smallpox.

The duration of the period of incubation of smallpox is remarkably constant. The initial symptoms come on, in a large majority of cases, on the eleventh or twelfth day, and the eruption appears on the fourteenth day. An interval of ten days only between the exposure and the initial symptoms is not very uncommon, and then the eruption appears on the thirteenth day. An interval of only eight days is rare, but Eichhorst has recorded three cases—one in a physician and two in students of medicine—in which the initial symptoms commenced in two of the individuals nine days and eight hours after exposure, and in the third nine days and four hours. So short an interval is rare, but when the disease is conveyed by inoculation the initial symptoms appear on the eighth or ninth, occasionally on the seventh day. The short periods are observed, it is said, more often in hot countries than in temperate climates, and there is some evidence that the incubation period of hemorrhagic smallpox is rather shorter than that of the discrete form of the disease. Longer intervals are rather more common—thus periods of thirteen, fourteen, and fifteen days between the exposure and the initial symptoms are not very rare, and cases have occurred which appear to prove that it may be prolonged to twenty days. These unusual periods must be taken into account in estimating the period during which a person who has been exposed to the infection should be kept under observation (*period of observation*) before it can be asserted that he has escaped. The Report of the Clinical Society gives fifteen days for this period, provided that the individual at that time shows no signs of indisposition and presents no elevation of temperature. The Code of Rules for the Prevention of Infectious and Contagious Diseases in Schools (hereafter referred to as the Code[s]) gives eighteen days. It will be safer, however, to put the period of observation at three weeks. The infection can be preserved for long periods in clothes and other fomites, and in the hair of a person who has been in intimate contact with a smallpox patient. Cases are on record in which the infection has thus been carried by nurses. In liberating a patient from observation, therefore, particular care should be taken that he does not then begin to use clothes which may have been in contact with the patient to whom he has been exposed.

The disease is infectious from the onset of symptoms until all scabs have become detached and until all desquamation has ceased; and great care should be exercised in any case in which some suppurating discharge is left as a sequel to the disease.

Chicken-pox.

The interval between the exposure to infection and the appearance of the eruption of varicella is usually fourteen days, and since the occurrence of prodromal symptoms is very inconstant, this must be reckoned the usual incubation period. It may be one day less, possibly in exceptional cases three days less. Longer intervals are far from uncommon, and a period of nineteen days has frequently been established. When produced by inoculation the incubation period is said to be ten days.

The period of observation is given in the Code as eighteen days, but it will be safer to prolong it to twenty days. Goodall and Washbourn[9] conclude from a consideration of five series of cases (nineteen cases in all): (1) That the incubation period of varicella is somewhat variable; (2) that it is never shorter than twelve days; (3) that it may be as long as nineteen, and is commonly longer than fourteen days.

During the period of incubation the patient presents no symptoms as a rule, but for a day or so before the eruption comes out there may be some malaise, and it is probable that infection may be contracted from the patient at this time. The patient continues to be infectious until convalescence is over and until all scabs have become detached. Infection can probably be carried by fomites.

Measles.

The duration of the interval between exposure to the infection and the appearance of the rash is usually fourteen days, but almost as often it is a day more or a day less. The pre-eruptive or prodromal stage is of uncertain duration; it may last only one day or may be extended to five days. The true incubation period of measles is therefore some two or three days as a rule less than the interval mentioned above. Probably in most cases it is eleven or twelve days. It is believed to tend to be short in cases in which the subsequent attack is severe with a high and long-maintained pyrexia (Bard), and on the other hand a long period of incubation is said to be followed usually by a mild attack. When produced by inoculation the period is said to be seven or eight days. During the period of incubation there are, as a rule at least, no symptoms, though Squire believed that in some cases there is a slight temporary rise of temperature about the sixth or seventh day of the period. I have never seen the least trace of this in any of the charts which have come under my observation.

The period of observation recommended by the Clinical Society's Report is fourteen days, and the individual must be at the completion of that time free from fever or catarrh. The Code fixes sixteen days, which is safer, as it would include nearly all even of the most exceptionable cases on record.

The infection of measles exists from the very earliest period of the developed disease, and is very intense, perhaps most intense, before the rash appears. There is no very notable diminution of the power of infection during the whole acute stage, and there can be no doubt that a patient may even be capable of conveying measles to another after convalescence has advanced far enough to allow him to go back to his usual avocations—to begin going to school again, for instance. Though there can be no doubt of this, it is equally well established that infection is far more often spread during the prodromal period. The period of isolation should extend to three weeks at least, and the patient should be free from all desquamation and cough before being allowed to mix with susceptible children. The infective principle has apparently little power of maintaining itself outside the body, and does not long survive in fomites, at least under ordinary circumstances.

Rubella (Rötheln).

The behavior of rubella presents a general resemblance to that of measles, but the incubation period is as a rule rather longer. As prodromal symptoms are not always present, or if present are often so slight as to escape observation, it is necessary to reckon the incubation period to the date of the appearance of the rash. This is given by the Clinical Society's Report as eighteen days, but it may be any period more than two and less than three weeks without being at all exceptional. In a considerable number of cases it is less than a fortnight by one or two days, and it seems necessary to admit that it is occasionally as short as five days. It seldom or never exceeds twenty-one days, though Baginsky[10] (on the authority of Buchmüller) admits twenty-four days. The duration of the period of observation should be, according to the Code, sixteen days, but as the incubation period may be as long as twenty-one days, the rule in the Clinical Society's Report—"two days more than three weeks"—is probably safer.

Rubella may be infectious for two or three days before the rash appears. It is in all cases infectious while the rash is out, but the validity of the infection declines rapidly, and in mild cases has probably ceased at the end of a week; in more severe cases it lasts longer, and risk cannot be regarded to have passed so long as any

desquamation continues. The Code prescribes "two or three weeks, the exact time depending upon the nature of the attack."

Scarlet Fever.

Scarlet fever usually comes on during the second or third day after exposure. Guinon, calculating the period as extending from exposure to the appearance of the rash, found that the incubation period was "invariably" four to five days, and quotes Sevestre and Johanessen in support of his observation. Reimer believed that in more than two-thirds of the 3,624 cases which he collected the disease came on within the first three days after exposure. Of 28 cases collected by the Clinical Society's committee in which the disease followed an exposure for a short time to a known source of infection, cases in which the facts were ascertained very carefully, in 16 the earliest symptoms were observed before the end of the third day, and in 10 of these before the end of the second day. In 2 cases the interval was seven days, and in 1 eight. Including other cases in which the interval between the commencement of the exposure and the onset of the disease was ascertained with precision, there were altogether 106 cases, of which number 52, or nearly half, began before the end of the third day after exposure, while 47 began on the second or third day. Eight days must be taken to be the extreme limit of the period, although certain authors have accepted periods much longer, extending even to seventeen days; but the true explanation of such cases is probably either that there has been a second exposure or that the patient had come into contact subsequently with clothes or other fomites soiled by the person first attacked, but not used until the period of convalescence is reached. The period of isolation given in the Code is fourteen days, but ten days would probably be sufficient if care were taken to make certain that the person was free from all fever and sore throat, and if all fomites which have been in contact with the infection be disinfected.

Scarlet fever is infectious from the appearance of the earliest symptoms and until desquamation has ceased and all signs of inflammation of the mucous membranes have passed away; the infection may be conveyed by the suppurating discharge of middle-ear disease until a late period. The period of isolation should be not less than six weeks, and the patient should receive a series of baths, and should not then be liberated unless "desquamation have completely ceased, and there be no appearance of sore throat" (Code). Owing to the fact that the infection is easily retained for long periods in fomites, it is necessary to practise most careful dis-

infection of all clothes, not only those used while the disease was coming on, but those which have been in the same room as the patient during the attack and during convalescence, of all bedding, of linen soiled by excretions or discharges, and of books and toys used during convalescence. Under exceptional circumstances, however, the individual may still be actively infectious as long as eight weeks after the commencement of an attack, and it is not safe to lay down any hard-and-fast rule on which laymen can be allowed to act on their own responsibility. The infection may be contracted from the body of a person who has died of the disease. With regard to the relation of scarlet fever to traumatism and to the puerperium, the facts are probably best summed up in the following sentence extracted from the Clinical Society's Report: "There is no proof that the period of incubation is shorter or longer in persons who have met with an injury, nor in women who have recently been delivered, but there are grounds for believing that the occurrence of labor or of traumatism may determine the onset of scarlet fever in persons who have previously been exposed to infection without taking the disease."

Diphtheria.

The usual period of incubation of diphtheria of the throat or larynx is two days, and it does not often exceed four days, although it occasionally reaches seven days. Probably it never really exceeds this period and is seldom less than two days. The Code gives twelve days as the period of observation, and this will be ample if the infection is really being spread by personal intercourse and not by other means, for it must be borne in mind that the infection of diphtheria can be conveyed by contaminated clothes and may hang about a house in carpets, beds, etc., for months or perhaps years.

A person may be infected by a patient in the incubation stage during the whole of the attack, and for a period of long but uncertain duration after apparent recovery. These conclusions, reached by the study of the history of cases observed clinically, are fully confirmed by bacteriology, which has shown that the specific bacillus may persist in the throat for many weeks and even for months. As a rule, in instances in which infection has thus been transmitted at a late period after the symptoms of the disease have passed away, some unhealthy condition of the tonsils or pharynx has persisted, and all cases in which such morbid states continue after an attack of diphtheria should be regarded with much suspicion as possible sources of infection to susceptible children brought into intimate relation with the sufferer. The infection may be contracted by intimate contact with the body

of a person who has died of the disease; the custom of allowing children to "kiss the corpse" is one which ought to be absolutely forbidden. The period of isolation after an attack of diphtheria which has been found satisfactory by the Medical Officers of Schools Association is not less than three weeks when convalescence is completed, provided that there be then no longer any form of sore throat, nor any kind of discharge from the throat, nose, eyes, ears, or other parts, and no albuminuria. The termination should, in fact, depend on the disappearance of all local lesions and of the bacillus from the throat.

Whooping-Cough.

The duration of the period of incubation of whooping-cough is somewhat uncertain, owing partly to the circumstance that the onset of the disease is usually insidious, and partly to the fact that in all probability the period actually varies a good deal. The usual period between exposure to infection and the beginning of catarrhal symptoms is seven to ten days; the characteristic whoop appears five to seven days later as a rule, so that the interval between exposure and whoop is usually about a fortnight. The period of observation recommended by the Code is twenty-one days, but probably fifteen days would be sufficient if the individual were examined carefully at the expiration of that period and found to be free from all trace of catarrh of fauces and pharynx and of all signs of bronchitis.

The infectiousness is marked in the earliest stage and before the characteristic whoop begins; it declines rapidly after the acute stage has passed. Weill, who in 1894 expressed the opinion that whooping-cough is contagious only during the premonitory catarrhal stage, has since[11] put his opinion to the test. On various occasions he permitted nearly one hundred young children, who had not previously suffered from whooping-cough, to be associated in the same ward for twenty days or more with children suffering from the disease during the stage of whooping. In only one case was the disease contracted, and in this instance the patient from whom the infection was derived was in the very earliest period of the whooping-stage. In three small epidemics he was able to satisfy himself that infection was contracted from children who had not yet begun to whoop. Weill concludes that infection ceases very soon after the characteristic whoops commence, and that therefore in a family it is not the patient who is already whooping, but his brothers and sisters who have not begun to whoop, that ought to be isolated. Those who have not the faith of this physician will do well to be guided by the recommendation of the Medical Officers of Schools Code, which is that the child should be kept isolated

from susceptible persons for six weeks from the commencement of the whooping, and should then be allowed to mingle with others only if the whooping and all characteristic spasmodic cough have ceased. If all cough have completely passed away earlier, which is not often the case, this rule may be relaxed and the period of isolation shortened.

Mumps.

The incubation period in epidemic parotitis is long. As the prodromal symptoms are not always present, and when present are often slight, it is necessary to reckon the period of incubation as extending from the moment of exposure to the onset of the parotitis. The usual period is three weeks, but periods of nineteen, eighteen, and seventeen days are very frequent. There is some evidence that the period tends to be shorter when the person infected has been exposed to the source of infection continuously or at least for several days at the commencement of the illness of the infector. The shortest period is probably fourteen days, though some writers (Biedert, Demme) have believed that it might be only eight days. The longest known period is twenty-five days. The period of observation mentioned by the Code is twenty-four days, but it would probably be safer to extend this by a day.

Mumps is very infectious at the earliest stage, and during the prodromal symptoms if they occur. This stage should be taken to last four days (before the parotids begin to swell), although it is not often so prolonged. The risk of infection diminishes progressively from the onset of parotitis, and as a rule has ceased three weeks after that date, probably in most cases in a fortnight, if all swelling of the parotids (and testicles if this occur) have subsided. The Code directs isolation for four weeks, when the patient may mix with others "if all swelling have subsided." Mumps is an extremely troublesome epidemic in schools, especially boys' schools, and it may be useful to bear in mind the following points: Firstly, that as mumps is infectious in the prodromal stage, persons who have been in contact with the first patient during this stage, which must be assumed to comprise the four days before the onset of the swelling even though no illness has been complained of, must be regarded as possibly infected and kept under observation; by isolating persons first seen ten days after exposure to infection, it may thus still be possible to limit the spread of the infection by such persons, even if they subsequently develop the disease themselves. In the second place, since the incubation period is most commonly nineteen to twenty-one days and is sometimes twenty-four or twenty-five, it is well

worth while to isolate a person who has been exposed to infection a fortnight or even three weeks earlier. In the third place, the isolation of mumps is easy, since the infection does not appear to be readily carried far from the body of the individual affected. Confinement of the patient to his own room is commonly effective in preventing spread through a household, if other children are really excluded from all communication.

Typhus Fever.

The incubation period of typhus fever is usually twelve days (Murchison[12]), but shorter periods are by no means rare, and many well-authenticated cases of a period of eight days are on record. Murchison accepts the belief that typhus fever occasionally follows in a few hours a very full exposure to the infection, and J. W. Moore,[13] of Dublin, states that in his own person he has often suffered from "a 'typhus headache' almost immediately after exposure to the poison of this disease." Murchison states that in his own second attack the period of incubation was "exactly five days." The longest known period of incubation of typhus fever appears to be twenty-one days, the duration in one of Murchison's cases. But instances of periods approaching this length are rare. A period of observation of three weeks completed may therefore be considered sufficient if the patient be in good health at its termination.

The infection of typhus is very virulent, but the area through which it operates is limited. Murchison believed that it was most infectious from "the end of the first week up to convalescence." During the first week of the fever there is comparatively little danger, and if the patient be isolated within that time others do not often contract the disease. Infection ceases when the appetite and digestion are restored. The average duration of an attack of typhus fever is about two weeks (13.43 days), and of five hundred cases that recovered in not one did the duration of the illness exceed nineteen days. Three weeks would therefore appear to be a sufficient time for isolation. The infection, however, clings to clothes, so much so that it has been supposed that typhus fever is most infectious during convalescence, the real fact being that the infection in the cases on which this opinion was founded was derived from clothes which the convalescent then again took into use. Clothes worn at or about the time of the onset of the disease, and bedding used during the attack ought therefore to be disinfected or destroyed.

Typhoid Fever.

The determination of the incubation period of enteric fever has always presented much difficulty owing to the paucity of cases affording evidence bearing on the point, and the difficulty of settling exactly the date at which an attack begins. During the period of incubation the patient is apt to suffer from various ill-defined symptoms, malaise, headache, pains in the limbs, and this condition merges gradually into the developed attack. In other cases, however, the onset of the disease is sudden, and the Report of the Clinical Society (for which all the reports on outbreaks of enteric fever made to the Local Government Board in England by its medical inspectors down to 1890 were analyzed) has provided a considerable mass of information, which is found to confirm the opinion of the best authorities published previously to that date. Cayley writing in 1884,[12] stated that "the common period is from ten to fifteen days. I have not found any well-authenticated case in which it was certainly less than five days or more than twenty-two days." The conclusion of the Clinical Scoiety's Report is: "The interval between exposure to infection and the development of distinct symptoms is probably most often twelve to fourteen days; it is not very infrequently nine or ten days, occasionally eight, and possibly less. . . . In rare cases it is prolonged to fifteen, eighteen, or even twenty-three days." No evidence was obtained to support Murchison's[12] belief that it might be as short as one or two days, and the cases upon which he relied do not bear close investigation. The theory that the period of incubation may be shorter when the "dose" of the infection imbibed with the ingesta has been large has been referred to above.

A patient suffering from enteric fever is capable of transmitting it to others throughout the whole course of his illness from the date of the earliest symptoms down to the end of the second week of convalescence at least, and his capability returns during a relapse. Infection can be conveyed by fomites, and retained by them for two months at least; washerwomen have frequently been infected by washing the linen of patients, the nature of whose disease has not been recognized at first, so that no disinfection was practised. In the majority of instances, in epidemics at least, the infection is not derived directly from the patient but indirectly through the medium of water or milk. With regard to the period of observation in such cases, experience appears to show than an epidemic due to contamination of milk with the specific infectious agent will most probably come to an end at or about the end of the second week after the supply of the infected

milk for consumption has been stopped. When water is the distributing medium a much longer time may elapse before cases cease to appear. Thus when a public water supply has been contaminated cases have often continued to occur until the fourth week after the source of the specific pollution has been removed, and in the cases of well-water the length of time is apt to be very much greater, owing probably to the fouling of the soil and the difficulty of insuring that disinfection has been thorough. The period of observation, therefore, is somewhat uncertain, and if the water supply cannot be entirely changed, it should extend over a month at least.

Relapsing Fever.

When inoculated in man the incubation period of relapsing fever is never more than eight nor less than five days. When contracted otherwise Murchison found that the incubation period was seldom more than nine days, that in few did it exceed twelve days, that the longest period which could be accepted was fourteen or possibly sixteeen days, and that in a considerable number of cases it was not more than five days, in some possibly less. It has been said that the fever has commenced immediately after exposure, but Cayley suggests that statements to this effect are due to errors of observation; such errors, considering the circumstances under which this fever prevails, are very liable to our.

Dengue.

The usual period of incubation of dengue is probably four days, but it may be extended to five days, and is not infrequently no more than three. It has been said to come on a few hours after exposure, but when an extensive epidemic prevails the chances of an error of observation are, as is the case with influenza, very great. The period of observation should therefore be about six days and of isolation about eight days, since the whole attack lasts seldom more than a week. The infection is extremely diffusible, and susceptible persons in a community visited by an epidemic seldom escape. One attack confers a very imperfect immunity.

Influenza.

The incubation period of epidemic influenza is short. The usual period is probably two or three days. The Clinical Society's Report concludes that it varies from one day or a few hours less, to four or five

days, but that the usual period is three or four days. It is probable that this makes the period rather too long, and that Parsons'[14] estimate of two or three days is nearer the mark. F. Widal puts the maximum period at two days, but this is certainly too short, though a very large proportion of cases do occur within that period. Periods as long as seven days have been reported, but during an epidemic of influenza it is exceedingly difficult to exclude the possibility of unrecognized exposure owing to the number of ambulatory cases, and of mild attacks which the sufferers call common colds, and for which they do not undergo any period of isolation. The period of observation should be six or seven days.

The patient is infectious throughout the acute attack, and may continue infectious until convalescence has advanced far enough to permit him to return to his ordinary avocations, and it is probably in this way that influenza is most generally spread. The period of isolation ought to be a week to ten days after the commencement of the disease, according to the severity of the attack. In cases complicated by pneumonia it should be extended to the end of convalescence.

Yellow Fever.

The usual incubation period of yellow fever is four days, or a day more or less. It may extend to seven days, and a period of fourteen days is admitted by Sternberg (Davidson[15]). The period may be as short as twenty-four hours, which has been accepted by Bemiss,[16] who, however, states that in three cases in which he was able to fix the hours of first exposure with precision, the attacks followed in seventy-two, eighty-three, and one hundred and one hours respectively. The period of observation ought to be a fortnight at least.

The infection is probably seldom derived from a patient direct, but it is easily contracted from fomites in which it may be preserved for long periods, or from the structure or fittings of foul ships. The bacillus described by Sanarelli,[17] which there seems to be good grounds for regarding as the infective agent, is very resistant to drying, but is easily killed by direct sunlight. Under certain conditions which would appear to be particularly liable to be produced on shipboard, it may be called into activity when otherwise unable to flourish by the growth in its vicinity of certain moulds, a fact which may account for the manner in which the infection has clung to ships, springing into activity at irregular intervals.

Asiatic Cholera.

The incubation period of Asiatic cholera varies between a few hours and a week, or possibly a little longer. Such extremes are, however, rare. The usual period is from two to five days. During the Dongola expedition of 1896 (Gallwey[18]) a party of soldiers were, there was good reason to believe, infected by bathing in the Nile at a point where a case of cholera had occurred in a boat on the previous day; one soldier was admitted to hospital on the next day, thirteen on the second day, fifteen on the third day, and one or two cases occurred down to the seventh day after the bath, when this outbreak ceased. The period of observation should be eight days.

The infection is seldom derived through direct intercourse with a patient. Water is the chief vehicle of the infective agent, which may also contaminate milk and various articles of food, such contamination being brought about mainly by way of water used in the "preparation" of the milk or food for sale or consumption. Vegetables may thus become contaminated during the process of washing. The main point in the prophylaxis of cholera, therefore, is the destruction of the cholera organism in the stools. Linen soiled with cholera evacuations easily carries the infection, and, as in the case of enteric fever, washerwomen are particularly liable to be among the earliest sufferers in an epidemic. The patient should be isolated until his stools assume a healthy appearance, and his stools should be disinfected or destroyed for one or two weeks longer at least, unless it be possible to resort to bacteriological examination to prove the absence of the cholera vibrio.

Bubonic Plague.

The incubation period of bubonic plague is seldom less than three or more than six days. This is the opinion of Lowson from his experience in Hong-Kong, and it is quoted with acquiescence by Cantlie,[19] who points out that the opinion of Aoyama, who assigns two to seven days, very nearly coincides. Bitter[20] from observations in Bombay arrived at the conclusion that the incubation period was between three and five days, but that it might last longer, though he did not believe that it ever exceeded ten days. Very short periods have been mentioned by some writers, but they are not well authenticated. The incubation period of plague during epidemic periods may therefore be taken to be usually some period between three and six days. Possibly an inter-epidemic periods, or if the individual be removed from the epidemic area, the interval between the exposure and the

onset of acute symptoms may be much longer, but in many of these cases the patients will be found to have been suffering from indolent bubo possibly due to the presence of the infective agent of true plague in a modified state of virulence. Rogers Pasha[20] places the period of observation at five or six days, but the International Sanitary Conference at Venice (1897) adopted ten days.

The specific microbe exists in an active pathogenic state in the various morbid secretions, in vomited matter and in the intestinal discharges, in the urine and the blood. The danger is particularly great from those cases in which pneumonia is the chief lesion, since the expectoration is copious and frequent and the sputum contains the bacillus in large numbers and in almost pure culture. In cases characterized by bubo alone the risk of infection is not great, especially if the bubo be not opened until suppuration is well established, and with the establishment of suppuration the plague bacillus is gradually destroyed. In other cases the patient should be isolated until all expectoration, diarrhœa, or other discharge has ceased. The clothing, furniture, and rooms occupied during the illness should be thoroughly disinfected. The bacillus is retained for some time in the bodies of persons who have died from the disease. It is easily destroyed by drying, particularly at high air temperatures, but it can survive for some days in clothes if moist, and in moist soil, and is liable to be disseminated when this soil is disturbed.

Malarial Fever.

The period of incubation most commonly observed is one of ten to fifteen days, the extremes being probably six and twenty-one days.[15] The shorter the interval between the paroxysms in the fever when it first develops the shorter also probably the period of incubation. Thus it is shorter in tertian than in quartan. When it has been induced by injection of malarious blood into healthy persons the disease has appeared at periods varying from six to sixteen days.

Bibliographical References.

1. Max Neisser: Zeitschrift für Hygiene, 1897.
2. Max Flesch: Berliner klinische Wochenschrift, October 28, 1895.
3. Kanthack and Stephens: Transactions of the Pathological Society of London, vol. xlvii., p. 361.
4. Roger et Gaume: Traité de Médecine de Charcot, Bouchard et Brissaud, t. i., p. 153.
5. Roque et Lemoine: *Ibidem*, t. i., p. 757.
6. Ballard; W. H. Power: Quoted in the Report of a committee appointed by

the Clinical Society of London to investigate the periods of incubation and contagion of certain infectious diseases, London, 1892.

7. Washbourn: Proceedings of the Royal Medical and Chirurgical Society, London. Meeting of November 26, 1895.

8. Code of Rules for the Prevention of Infectious and Contagious Diseases in Schools, issued by the Medical Officers of Schools Association, London, 1886.

9. Goodall and Washbourn: British Medical Journal, 1896, ii., 741.

10. Baginsky: Lehrbuch der Kinderkrankheiten, fifth edition, p. 165.

11. Weill: Lyon Médical, May 9, 1897.

12. Murchison: Treatise on the Continued Fevers of Great Britain, third edition, edited by W. Cayley; also St. Thomas's Hospital Reports, vol. ii., 1871.

13. J. W. Moore: Text-book of the Eruptive and Continued Fevers, Dublin, 1892.

14. Parsons: Report on the Influenza Epidemic of 1889-90. Local Government Board of England, 1891, pp. 63 *et seq.*

15. Davidson: Hygiene and Diseases of Warm Climates, London, 1893.

16. Bemiss: Pepper's System of Practical Medicine, vol. i., p. 643, Philadelphia, 1885.

17. Sanarelli: Annales de l'Institut Pasteur, June 25, 1895.

18. Gallwey: Cholera Report of Frontier Mudiria and Dongola Expeditionary Force, 1896.

19. Cantlie: British Medical Journal, 1897, i., 73.

20. Report of the commission sent by the Egyptian Government to Bombay to study the plague, Cairo, 1897.

SMALLPOX.

BY

JOHN WILLIAM MOORE,

DUBLIN.

SMALLPOX.

Synonyms.—Variola (from *Latin:* varus, a blotch, a pimple); *French:* La petite vérole, picote (a man marked with smallpox is said to be *picoté*), variole; *German:* Blattern, Menschenpocken; *Italian:* Vaiuolo; *Spanish:* Viruelas; *Danish* and *Norwegian:* Kopper; *Swedish:* Smittkoppor; *Arabic* (Rhazes): Jadarí; *Modern Greek:* Εὐλογία (a euphemism); *Irish:* Bolgach (pustules or blisters), galar-breac (the speckled disease). "Pox" is one of the plural forms of "pock," derived from the Anglo-Saxon *poc* or *pocc*, a bag or pouch, poke or pocket. Chaucer has this line—

"Of *pokkes* and of scab and every sore."

In Scotland the disease is called "the pocks" to the present day, the reference being to the pokes or pockets of matter which constitute the true rash in its mature stage. The English term "smallpox" was introduced at the end of the fifteenth, or early in the sixteenth century, with the object of distinguishing the disease from syphilis, or the "great pox." The word was first used by the old chronicler Raphael or Ralph Holinshed, who died about the year 1580.

Varioloid is modified smallpox—the result of (*a*) a previous attack, (*b*) inoculation, (*c*) vaccination. In this variety of the disorder the febrile movement is usually moderate, and there is little or no secondary fever—a condition which will be afterwards explained.

Definition.

An acute specific, infectious febrile disorder, setting in suddenly with chills, headache, backache (severe pain in the lumbar and sacral regions), sweating, vomiting, and tenderness on pressure in the epigastrium. Smallpox is characterized by a certain typical range of temperature, a specific inflammation of the skin (dermatitis), and often one of the mucous membranes also. An early, or prodromal, fever of short duration and a continued type is followed by a remission, to which in turn succeeds a secondary fever, relapsing in character and more or less prolonged in proportion to the amount of suppuration that is present. The dermatitis is shown by the development, usu-

ally on the third day, of a papular or pimply rash, which quickly becomes vesicular and finally (in many of the severer cases) pustular. In this stage there is often great swelling of the face, hands, and feet. The appearance of the rash is followed by a fall of temperature, but a secondary fever accompanies the development of pustules at the end of the first week. These pustules finally dry up (desiccation) and form foul-smelling, highly infectious crusts or scabs, which are shed or cast off about the eighteenth day. The disease is not infrequently complicated with hemorrhages into the skin (purpuric smallpox) and from the mucous membranes (hemorrhagic smallpox). These hemorrhages may occur early and interfere with the development of the true smallpox eruption; or late, constituting *Variola hæmorrhagica pustulosa* (Curschmann). Secondary infections are apt to accompany or follow the disease, leading to dangerous complications or sequelæ.

History.

The origin of smallpox is unknown. Its native foci may be looked for in India and in the countries of Central Africa (August Hirsch). From these original seats its diffusion over the earth's surface has been brought about by successive importations of the morbid poison. At the present time the dominion of smallpox extends over almost the whole inhabited globe, and only a few isolated regions still enjoy a complete immunity from it. According to Holwell,[1] traditions have existed in the Brahmin caste from time immemorial concerning the prevalence of smallpox in India. There has existed in that country from the earliest times the temple worship of a deity whose protection and help were invoked on the epidemic outbreak of the disease. In the Atharva Veda a description of this temple service is contained, together with the prayers used by the Brahmins at the inoculation with smallpox, which has been practised there from the remotest antiquity. Wise, in his "Commentary on the Hindu System of Medicine," gives a sketch from the oldest Sanskrit writings on medicine (the Charika and Susruta) of the spotted and pustular skin diseases, and among them of the smallpox, which he is convinced had been prevalent in India from a very remote period. In a paper entitled "Marwar, the Land of Death," the late Sir W. J. Moore, K.C.I.E., wrote many years ago: "The people firmly believe variola to be under the control of the goddess Matha, in whose honor temples abound throughout Marwar and fairs are even held at Joudpoor. Near the latter city is a space of ground filled with trees, called 'Kagli ka Bagh,' and containing the 'Setla Deir' (or smallpox-god's shrine). In the month of March a *mela* is held here in honor of

Matha, and thousands of women and children attend with offerings for the goddess. The declivities of most of the numerous conical hills present either a reddened stone or a temple devoted to Matha, with most probably an attendant Brahmin priest. Nearly every village has its goddess of smallpox in the immediate locality, and a large piece of ground is esteemed as holy, and called 'Matha Ka Than.'"

In his work on "Climate and Medical Topography in their Relation to the Disease-Distribution of the Himalayan and Sub-Himalayan Districts of British India" (London, 1880), Dr. F. N. Macnamara tells us that the mortality from smallpox has vastly decreased of late years (he wrote in 1879) in the province of the Punjâb. This result must be ascribed to the active operations of the Vaccine Department and the steady subsidence of the prejudice against vaccination in most of the districts. To the latter factor there is one notable exception. In the districts of Goorgaon, Kurnaul, Rohtuck, and Hissar, situated along the Jumna River, in the southeastern angle of the province, smallpox still rages. In these districts an unabated opposition to vaccination is due to the preponderance of the Hindoo element in the population. In Goorgaon is a famous temple to Seetla, the goddess of smallpox, to whom thousands of victims are literally sacrificed year by year. The Sanitary Commissioner of the Punjâb, in his Sanitary Report for 1877, shows that of the total deaths from smallpox during that year—namely, 12,296—2,934 occurred among children under one year of age, 9,835 among children aged between one year and twelve years, and only 517 were among adults.

Dr. de Renzy, in his report for 1873, points out that the disease year by year attains its maximum of fatality in May, and then steadily declines until the minimum is reached in October, when it again becomes gradually more fatal month by month until the maximum is reached.

An equally great antiquity for the diffusion of smallpox in China was claimed by James Moore, of Glasgow, the historian of the disease at the beginning of the nineteenth century,[2] on the authority of a Chinese treatise written long before Christ and entitled "Teontahinfa" ("Heart Words on the Smallpox"). In this work the first appearance of the disease in China is referred to the time of the Tsche-u dynasty, or the period between 1122 and 249 B.C. In a short article on "Smallpox in China,"[3] Mr. F. Porter Smith tells us that the disease dates from the reign of the first emperor of the (Eastern) Han dynasty, Kwang Wu, who reigned A.D. 25–28. It is said to have been imported from some part of Central Asia or of Southwestern China by Chinese troops returning from a campaign. Certain it is that inocu-

lation has been practised among the Chinese for a thousand years or more. Lagarde[4] puts the antiquity of smallpox in China at upwards of two thousand years. According to F. Porter Smith, the disease is called in Chinese *Tien-hwa*, which means "the heavenly flower," and it has been deified, temples being erected in all parts of the empire in honor of the goddess, who bears the name of "Holy Mother of Smallpox."

Hirsch confesses that the question of the antiquity of smallpox in African countries is entirely beyond our answering; nor on European soil can the occurrence of the disease be traced back with certainty beyond the Christian era. It is generally believed to have first shown itself at Pelusium in Egypt, A.D. 544 (Procopius: "De Bello Persico," Lib. ii., cap. 22), and to have thence spread over Egypt, Syria, and Asia Minor. According to Curschmann[5] this view must be abandoned, for the epidemic in question has come to be regarded as one of true bubonic plague. The diffusion of smallpox, eastward and westward, was probably effected by the Saracen armies, led forth to conquest by Mahomet at the era of the Hegira, A.D. 622. But many years prior to this date, in A.D. 581, we have an account by Gregory of Tours of an epidemic which, from the description of that chronicler, Curschmann considers was certainly smallpox. It raged over almost the whole of southern Europe and was described as "Lues cum vesicis," "Pustula," "Pustulæ," or "Morbus disentericus cum pustulis." The real bubonic plague, which broke out at Narbonne in the year 582, was carefully distinguished from it by Gregory, under the name "Morbus inguinarius." A few years previously also, A.D. 570, an epidemic of smallpox was widely prevalent in France and Italy. This was described by Marius, of Avenches, who uses the term "variola" for the first time to designate the disease.[6]

To the Arabians, and among them especially to Rhazes (A.D. 900), we owe the first reliable and scientific description of smallpox. In his treatise "De Variolis et Morbillis," Rhazes conveys that Galen was familiar with the disease, and he quotes fragments from the "Pandects" of the Alexandrian physician, Ahron, dating from the fifth or sixth century, which go to prove that he too was well acquainted with it.

Among Latin writers on smallpox, the first of any authority was a Salernian physician, Constantinus Africanus by name, a native of Carthage, who had been educated in Arabian schools.[7] He was the first to restrict the word "variola" to smallpox. A diminutive of the Latin "varus," a pimple, the term had previously been used to denote other skin affections than smallpox which were attended by the formation of papules and pustules.

The disease invaded the British Islands a some time between the tenth and thirteenth centuries. Curschmann gives the date as 1241–42. Ralph Holinshed, who described a great epidemic which occurred in the reign of Edward III., writes: "Also manie died of the *small pokkes*, both men, women, and children." In the Netherlands the first account of it comes down from the tenth century. In Denmark it must have been already prevalent in the thirteenth century, for Iceland received the infection from that country in 1306 (Hirsch). Germany and Sweden became infected towards the close of the fifteenth century. In Europe generally smallpox was one of the most widely distributed, most frequent, and most destructive of pestilences up to the introduction of vaccination at the close of the eighteenth century.

Lord Macaulay, writing of the death of Queen Mary in 1694, thus describes the ravages of smallpox: "That disease, over which science has since achieved a succession of glorious and beneficent victories, was then the most terrible of all the ministers of death. The havoc of the plague had been far more rapid; but the plague had visited our shores only once or twice within living memory; and the smallpox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover."

The Western Hemisphere received the infection first in 1507, fifteen years after the discovery of America by Christopher Columbus. Mexico was devastated by the malady in 1520 after the arrival of troops from Spain. It was not until the seventeenth century that the United States were reached by smallpox. Australia enjoyed complete immunity from its ravages until 1838, when it was imported into Sydney, probably from China. It did not spread extensively, and the Australian colonies are now practically free from the disease. Tasmania and New Zealand have never suffered from it, but it has raged from time to time in many of the island groups of Polynesia. Into South America, and particularly into Guiana and Brazil, smallpox has been more than once introduced by negro slaves from Africa. Brazil, La Plata, Chili, and Peru have all from time to time suffered severely from its ravages. In Chili it is known to the people as "peste," κατ' ἐξοχήν (Fournier[9]).

All authors concur in testifying to the dreadful mortality occasioned in all countries by smallpox in pre-vaccination times, and to the consequent terror which its visitations everywhere excited. In the Middle Ages its death-toll could be counted by millions. Before

the introduction of vaccination—a little more than a century ago (1796)—the annual rate of mortality from the disease in England and Wales alone was three thousand in every million of the population. In 1890 smallpox caused only fifteen deaths in England, and the average annual number of deaths from it in the ten years, 1881–90 inclusive, was 1,227.8—that is, but one-seventieth part of the death-rate of pre-vaccination times.

Etiology.

To Boerhaave, of Leyden, belongs the credit of first assigning contagion as the proper exciting cause of smallpox. Hirsch is of opinion that there are two factors only which determine the recurrence of an epidemic of smallpox: on the one hand, the necessary number of persons susceptible of the morbid poison, and on the other

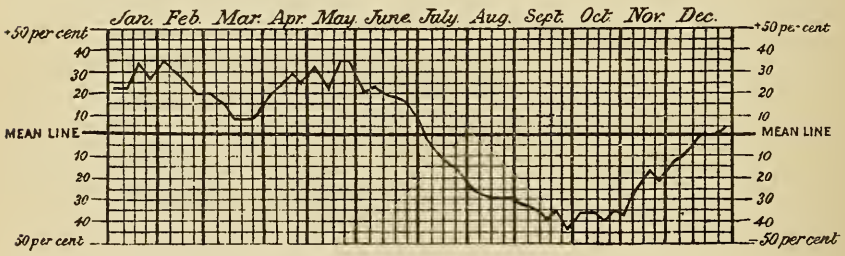

Fig. 1.

hand, the introduction of the specific virus itself. The malady shows a singular independence of climate and soil, thriving equally well whithersoever its contagium is carried, and wherever it finds a population open to its reception, being unprotected by a previous visitation, by inoculation, or by vaccination. It is this latter circumstance which explains the periodicity of smallpox epidemics in various districts or places.

Although the incidence of smallpox is apparently *independent of climate*, yet the *season of the year* has a marked influence upon the prevalence of the disease. Nearly all writers are agreed that, while outbreaks of smallpox may occur at all seasons, they mostly begin towards the end of autumn and in the early spring, or in the cold season. In a word, smallpox is essentially a *disease of winter and spring*. In the British Islands, and Western Europe generally, for example, the monthly number of cases is high from November onwards; but from May a rapid decline in the prevalence of the disease takes place, the least number of cases being observed in September.

The accompanying diagram (Fig. 1) is copied from the annual

summary of births and deaths of the registrar-general for England for 1890. It shows the weekly departure from the average weekly number of deaths from smallpox (seventeen) in London in the fifty years, 1841–1890, inclusive. In this diagram the thick horizontal line represents the mean weekly mortality from smallpox in London (seventeen), on the supposition that the mortality is spread equally over the fifty-two weeks of the year, the fifty-third week, when it occurs, being ignored. The curved line represents the amount per cent. by which the average mortality in each week differs from this mean. When the percentage for any week is above the mean, the amount of the percentage excess is marked above the horizontal line representing the mean, and when the percentage is below the mean, it is marked below the line.

It must be remembered that the data on which the curve is formed are the deaths registered in each week, not the deaths which occurred in the week, and that the registration is usually a few days after the date of death; and, secondly, that the curve relates to deaths—that is, the final termination of the attack of illness, and not its commencement. So that, in estimating the effect of season in generating smallpox, allowance must be made for the average duration of this disease when fatal—that is, eleven or twelve days. It is, moreover, possible that the curve of mortality may, for another reason, not accurately represent the curve of prevalence. For it may be that an attack of smallpox is more likely to terminate fatally if it occurs at one season —for example, midwinter—than if it occurs at another, such as midsummer.

The diagram shows that at the beginning of February and in the second half of May the weekly number of deaths was thirty-five per cent. in excess of the average weekly number of seventeen deaths represented by the mean line, whereas at the end of September there was a deficit of forty-three per cent. in the weekly number of deaths as compared with the same average weekly number over the whole year.

In Dublin, during the autumn of 1871, the prevalence of, and mortality from, smallpox increased with a fall of mean temperature below 50° F., and the greatest severity of the epidemic was experienced in the first half of the following April, shortly after a period of intense cold for the time of year. With the rise of mean temperature to between 55° and 60° in the middle of June, 1872, the epidemic declined rapidly. Abundant rainfalls seemed to be followed by remissions in the severity of the epidemic, and the converse was also true.[10]

Dr. Alexander Buchan and Sir Arthur Mitchell, of Edinburgh, say that the curve for smallpox is one of the simplest of the curves,

showing that the mortality from the disease is above the average from Christmas till the end of June, the maximum falling in the last week of May, and the minimum in the last week of September.

From statistics as to the prevalence of the disease in Sweden, by months, in the years 1862-69 inclusive, it appears that the greatest prevalence of smallpox is observed in May, the cases in that month being 13.7 per cent. of the total cases occurring in the year; while the least prevalence is observed in September, when only 3.9 per cent. of all the cases in the year occur. From November the monthly number of cases is high, but from May a rapid decline in the prevalence of the disease takes place.

These statistics were compiled from exhaustive annual reports by the late Dr. Wistrand, as to the morbidity of Sweden, and are the direct fruit of an admirable system of disease-registration, which has been in operation for many years in Sweden, and also in the other Scandinavian countries.

When due allowance has been made for difference of climate, these results agree very closely with the observations which have been recorded in this country on the relation of smallpox to season. The late Dr. Edward Ballard,[1] commenting on the epidemic of 1870–71 as observed in London, wrote:

"There is some reason for believing that the variations of the epidemic (of smallpox) from week to week are influenced to a certain extent by atmospheric conditions and more especially by variation in temperature."

He then quoted a series of remarkable coincidences between the fluctuations of mean temperature and those of the smallpox mortality in London during the winter of 1870–71. In the number of the same journal for May 13th, 1871, he wrote:

"The epidemic has now lasted a good six months. It may be regarded as assuming a distinctly epidemic form in November, shortly after the mean temperature of the air had fallen decidedly below 50°. In the progress of the seasons we have now arrived at a time when this mean temperature is again reached. The mean temperature of the last three weeks, as recorded at Greenwich, has been 50°, 50.7°, and 49.7°. It is customary about the second week in May for some check in the consecutive weekly rises of temperature to take place, but after this, in the ordinary or average progress of events, the steady rise towards the summer temperature may be expected to set in, and with it there is at least a hope that the epidemic will begin to fade."

A week later, the same writer said:

"The sudden fall of deaths in London from smallpox which oc-

curred last week, namely, from two hundred and eighty-eight to two hundred and thirty-two, occurring about three weeks after the mean temperature of 50° was reached, appears to be confirmatory of the favorable hopes we expressed last week, that the epidemic had, for this season, arrived at its climax."

And so it had, for although the decline was occasionally interrupted, the virulence of the epidemic was broken in May, in accurate fulfilment of the anticipations which had been grounded on a consideration of the influence of temperature on its progress.

From the foregoing observations it would appear that the critical mean temperature in regard to smallpox is 50° F. When the mean falls below that value, the disease spreads; when it rises above it, the disease wanes. The explanation is, no doubt, to be found in the fact that defective ventilation, overcrowding, and deficient nutrition wait upon cold weather, and these are the most powerful predisposing causes of smallpox no less than of typhus.

Individual susceptibility to the poison of smallpox extends to the whole of mankind, but experience shows that the colored races, and particularly the negro race, are—other things being equal—in greater risk from smallpox than the whites.[12] Not only in their own country, but in foreign lands also, the blacks retain this peculiar sensitiveness to smallpox contagion (Curschmann).

The susceptibility to the disease extends to all periods of life, although infants at the breast seem to be less prone to contract it than children over one year old. Even intrauterine life does not preclude the risk of infection. Curschmann, in his masterly monograph in von Ziemssen's "Cyclopædia of the Practice of Medicine," cites a remarkable instance which would go to prove that in such cases infection takes place rather by simple contact than through the mother's blood. A woman servant, aged twenty-two, in the fifth month of her first pregnancy, suffered from varioloid from November 28th to December 12th, 1870. On December 28th fœtal movements suddenly ceased. On the 31st a five to six months' child, evidently already some days dead, was born. It presented a well-formed smallpox rash in the stage of suppuration, covering the whole body —least marked on the face and most abundant on the back and buttocks. The appearances were such as to place the time of death (on December 28th) somewhere between the sixth and eighth days of the disease. This would give an incubation of at least ten to fourteen days, on the assumption that infection occurred towards the close of the mother's attack. Smallpox has been observed as early as the fourth month of embryonic life. Curschmann can vouch for its appearance at the fifth month of gestation from his own observa-

tion. Occasionally an apparently healthy mother (not attacked by smallpox during pregnancy) has given birth to a child affected with that disease. The fœtus has become infected through the exposure of a mother personally immune at the time. This is a possible explanation, but Curschmann considers that some of these infrequent cases may be explained on the hypothesis that the mother suffered from *Variola sine exanthemate*, and so became the source of infection to the child.

Sex does not appear to be an energetic predisponent to the disease, but males are on the whole attacked more commonly than females—no doubt because they are more exposed to the danger of infection in their several callings. Dr. John MacCombie, in his article on "Smallpox" in Clifford Allbutt's "System of Medicine" (1897), gives the following table, showing the sex and numbers of smallpox patients at different quinquenniads up to twenty-nine years of age ("Metropolitan Asylums Board Reports," London).

Age.	Male.	Female.
Under 5 years	799	717
5 to 9 "	1,211	1,209
10 " 14 "	1,659	2,029
15 " 19 "	2,389	2,087
20 " 24 "	2,206	1,556
25 " 29 "	1,337	941
30 years and upwards	2,075	1,482
Total	11,676	10,021

Pregnancy and *childbirth* do not materially predispose to smallpox, but in these physiological conditions the disease is apt to assume a severe type.

There is no reason to doubt the occasional coexistence of smallpox with either an acute or a chronic preëxisting malady, but the occurrence is rare. It is certain that the prodromal accidental rashes of smallpox have sometimes been mistaken for either scarlatina or measles. Curschmann asserts rather dogmatically that for an individual suffering from scarlet fever, measles, or typhoid fever, there is, throughout the entire duration of the affection, only a very slight liability to an attack of variola. His own experience, however, in the hospital at Mayence goes to show that *convalescents* from typhoid fever are distinctly susceptible to variolous poisoning. The same is probably true of convalescents from other infective diseases. The susceptibility of healthy individuals varies remarkably from time to time, even independently of vaccination or inoculation.

In general, one attack of smallpox confers upon an individual a lifelong immunity from a second. But this is not universally true, nor

can it be admitted that a second attack, when it does occur, is necessarily milder than the first. Louis XV. of France had smallpox when a lad in his fourteenth year. He died of a second attack in his seventy-fourth year. Trousseau mentions the case of a medical student who, though he bore the marks of two attacks of smallpox, took it a third time and that, too, in a rather severe form.

Bacteriology.

The *causa causans*, or exciting cause, of smallpox is the introduction into the system, by inoculation, inhalation, or possibly swallowing, of the specific virus or contagium of the disease. This we are led by analogy to regard as microbic in its nature. But even at the time of writing (1897), we are obliged to admit that the bacteriology of variola is as yet incomplete. According to Edgar M. Crookshank,[13] cocci .5 μ in diameter, singly, in pairs, and in long or short chains and colonies, have been found by Cohn in the fresh lymph of human vaccina and cowpox, and in the pustules of true smallpox. They are regarded as the active principle of vaccine lymph, since filtration deprives this of its infectious element (Chauveau). The Regius Professor of Medicine in the University of Oxford, Dr. Burdon Sanderson, confirmed this observation. The lymphatics of the skin in the region of the pustule of both human smallpox and sheep-pox (*Variola ovina*) are filled with cocci (Weigert and Klein). Successful vaccination has been stated by Quist to result from artificial cultivations. These cocci have been called Streptococcus variolæ et vaccinæ. Loeff and Pfeiffer have discovered in the blood of smallpox patients certain protozoa, to which they attribute a pathological significance.[14]

In the report of the medical officer of the Local Government Board (England) for 1892–93, Dr. E. Klein described a peculiar extremely minute bacillus, or rod-shaped microorganism, as occurring in calf lymph and in human variola lymph during the early phases —in the calf lymph seventy-two to ninety-six hours after vaccination, in the human variola lymph during the third or fourth day. In both instances the lymph was collected aseptically. In the bacilli, when abundant, forms were recognized in which some globules resembling spores existed. Calf lymph of later stages (five or six days old) showed no bacilli, or only here and there a trace. The presence of these spore-like bodies and the absence of bacilli in the lymph of later stages led Klein to conclude that in smallpox and the vaccine disease we have to deal with a spore-forming bacillus. The bacilli multiply in the early phases, spores are then formed, and it is these which prevail in the lymph of the later phases. This would

explain the preservation of the active principle of vaccine lymph in glycerin, which is a germicide for cocci and sporeless bacilli, but not for spores. It would equally explain the continued activity of vaccine lymph dried on ivory or bone points, for such prolonged drying would kill all but spores.

Dr. Klein's researches have apparently been confirmed and his views have received independent support through investigations carried out by Dr. J. Christian Bay, of Des Moines, Iowa, bacteriologist to the Iowa State Board of Health. This observer has obtained from vaccine lymph cultivations, in beef bouillon (one pound of meat to one litre of water) rendered alkaline with sodium chloride, of colorless, non-motile bacilli, with a long diameter measuring from .6 μ to 1 μ, and the short diameter from .2 μ to .3 μ. This organism was found, with three exceptions, in examinations of sixty-five cultures from vaccine points. These bacilli bear spores from an early stage of their development. Each organism contains two spores, one at each end. As this is the most conspicuous feature of the organism, Dr. Bay refers it to the genus Dispora, established in 1882 by Kern, and he calls it Dispora variolæ. The same organism was also found in the lymph from a case of confluent smallpox in the Smallpox Hospital, Chicago. Of forty cultures in bouillon made from this lymph, only two failed to show Bay's bacillus.

Smallpox is a typically infectious or catching disease. Most usually it spreads from person to person. It clings to articles of furniture or of dress, which in this way become fomites or carriers of infection. It may be conveyed through the medium of a person not himself ill of it. It may be caught from the dead body. "The dispersion of the morbid poison," writes Hirsch,[15] "takes place either by the smallpox patients themselves, or through the medium of other persons, or of articles to which it clings. It has been conclusively proved by very numerous and unambiguous observations that an atmosphere of smallpox poison develops around the sick, especially when they are crowded in close rooms; or, in other words, that the air may become a carrier of the contagion, so that the latter can be spread by the atmospheric currents within a small range. There is certainly no mathematical expression to be found for the extent of that range; at the utmost, it extends no farther than the immediate surroundings of the sick."

Although Hirsch thought that no mathematical expression can be found for the extent of the aërial convection of smallpox, yet the experience of recent epidemics in the British Isles proves that its *striking distance* is considerable, certainly much greater than that of

typhus fever. In the outbreaks of 1871–73 and of 1876–79, the question did not perhaps receive the attention to which it was justly entitled. A local epidemic in Sheffield in 1887 and 1888, however, afforded an opportunity of reducing the facts to a mathematical expression.

In his "Manual of Public Health,"[16] Mr. A. Wynter Blyth observes: "The usual spread of smallpox is from person to person, but

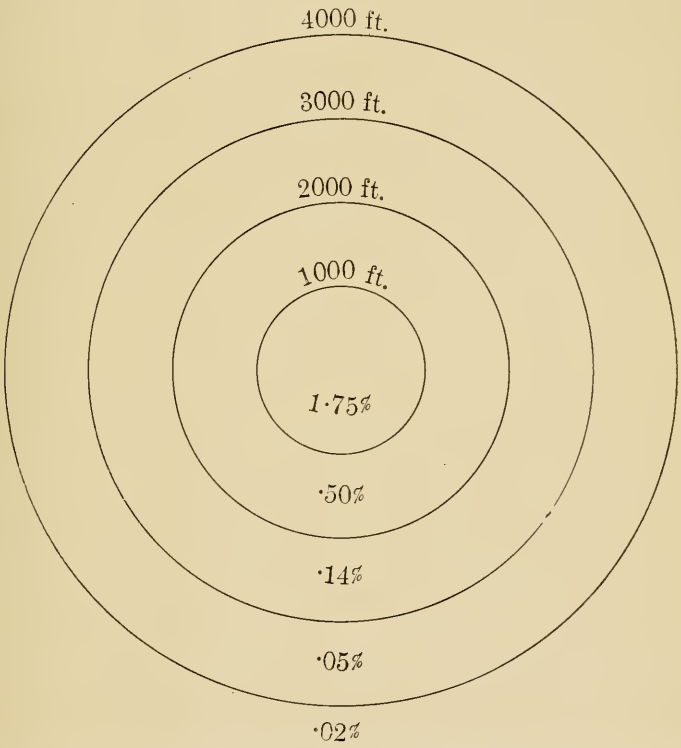

Fig. 2.—Diagram showing the Influence of the Sheffield Hospital in spreading the Disease in 1887-88.

from inquiries which have taken place as to the influence of smallpox hospitals upon a surrounding population, and the experience of the Sheffield epidemic (of 1887–88), it is certain that the infection can strike at a distance. Whether the contagious particles are conveyed by the air itself, or by the medium of the common household fly or other insects, the important fact remains that infection may travel far. The influence of the Sheffield Hospital could be distinctly traced for a circle of four thousand feet; for instance, the following percentages of households attacked at successive distances from the hospital

are given in the original report by the late Dr. F. W. Barry,[17] inspector of the Local Government Board for England:

"0–1,000 ft.	1–2,000 ft.	2–3,000 ft.	3–4,000 ft.	Elsewhere.
1.75	.50	.14	.05	.02

This possibility of smallpox spreading by aërial infection increases greatly both the hospital difficulty and that of individual isolation."

At the annual meeting of the British Medical Association, held

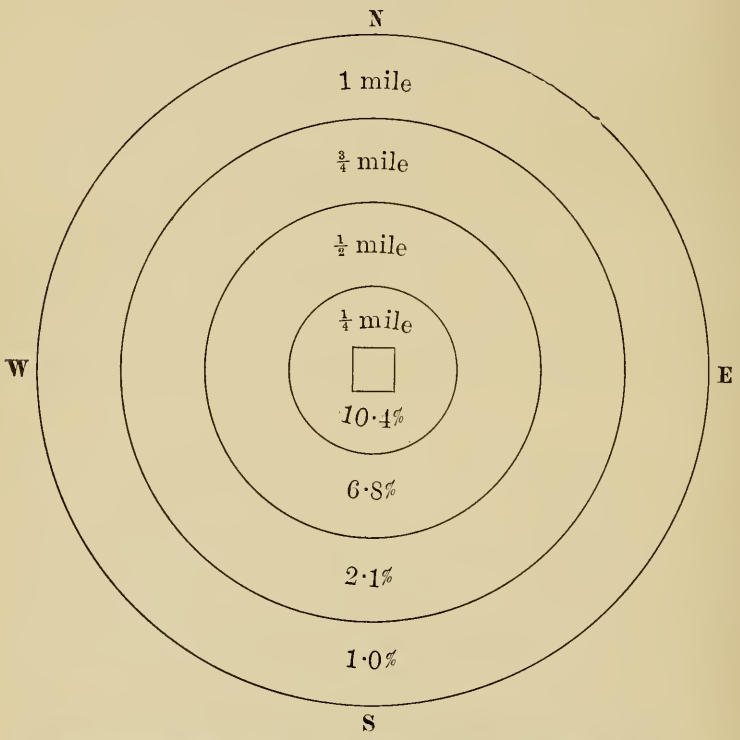

Fig. 3.—Diagram showing the Influence of the Bradford Smallpox Hospital on the Surrounding Neighborhood in Spreading the Disease.

at Bristol in 1894, Dr. Arnold Evans, of Bradford, Yorkshire, read a paper before the Section of Public Medicine on the aërial convection of smallpox. This author, from his personal observation of an outbreak at Bradford in 1893 confirmed the conclusions arrived at by Dr. Barry. He showed that between January 14th and December 30th, 1893, 626 houses became newly invaded by smallpox within one mile of the Bradford Fever Hospital, which was used during the greater part of the year named for the isolation of the disease in ques-

tion. The hospital is pleasantly situated on an eminence on the eastern side of the town, at an altitude of some four hundred feet above sea level. It covers about eleven and a half acres of ground. The one mile area round the hospital contains over 17,000 houses. Of the 626 houses newly invaded, 162 were situated under a quarter of a mile from the hospital, 242 within a ring between a quarter and half a mile distant from it, 163 in a ring within half a mile and three-quarters of a mile, and 59 in a ring within three-quarters of a mile and

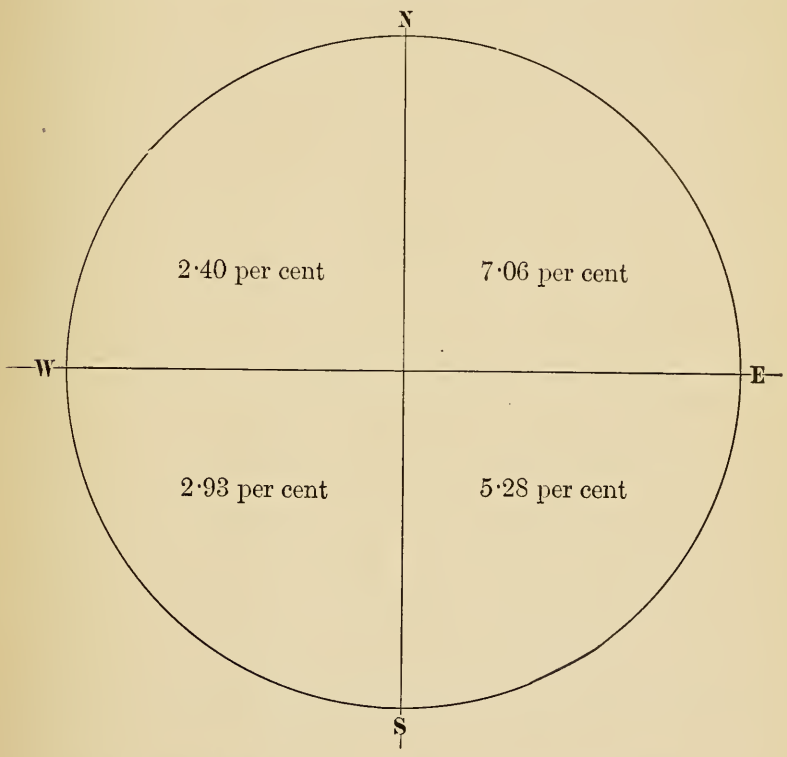

Fig. 4.—Diagram showing the Influence of Wind in Disseminating Smallpox.

one mile from the hospital. The rate of incidence of smallpox on 100 houses in the whole borough was 1.6; in the special area bounded by a circle of one mile radius from the hospital, 3.6; in the other parts of the borough outside the special area, 0.6. The rate on the total houses within a mile of the hospital having been 3.6 per cent., it was 10.4 per cent. on houses within a radius of a quarter of a mile, 6.8 per cent. within a quarter and half a mile distance, 2.1 per cent. within half a mile and three-quarters of a mile, and only 1.0 per

cent. on houses within three-quarters of a mile and one mile distance from the hospital.

Taking all things into consideration, it seems to Dr. Evans that the most likely way to account for the extensive prevalence of smallpox over the special area described is that the poison was conveyed aërially direct from the wards of the hospital. A study of the direction of the prevailing winds throughout the year 1893 supplies

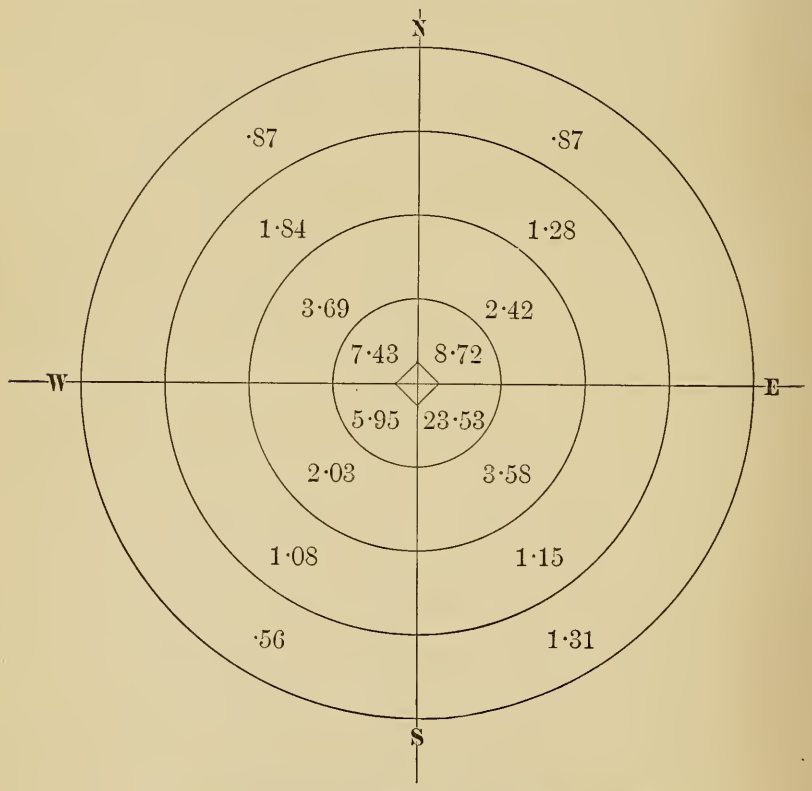

Fig. 5.—Diagram showing the Influence of Wind in Disseminating Smallpox.

strongly confirmatory evidence of this view. In order to demonstrate the influence exerted by the wind in determining which side of the hospital received for the longest period the infected air from the hospital wards, Dr. Evans divided each quarter-mile zone of the special one-mile area into quadrants, by drawing radii to north and south, to east and west. He thus ascertained the percentage of infected houses in each of the four quadrants lying respectively northeast, northwest, southeast, and southwest of the hospital. The results are striking.

In the northeast quadrant, 7.06 per cent. of the houses were infected; in the northwest quadrant, 2.40 per cent.; in the southeast quadrant, 5.28 per cent.; in the southwest quadrant, 2.93 per cent. A further calculation also shows that the percentage of infected houses in the special zone to the east of the hospital amounted to 5.6 per cent., as compared with 2.9 per cent. on the west side. These figures are easily explained by the fact that on two hundred and fifty days of the year the prevailing winds were westerly, and only on eighty-

FIG. 6.—Diagram showing the Influence of a Smallpox Hospital on the Surrounding Neighborhood in Spreading the Disease.

three days was the wind persistently from the east. During the first half of the year, when easterly winds were more common than during the second half, the proportion of cases occurring on the western side of the hospital was relatively greater than during the remainder of the year, when east winds were less frequent.

The facts which have been quoted relative to the outbreak of 1893 in Bradford are graphically shown in the Figs. 3 and 4, which are reproduced from the last edition[17a] of Parkes' "Hygiene."

The following figures are brought out in a report on the Fulham

outbreak by Mr. W. H. Power, inspector of the Local Government Board of England. The outer circles in Figs. 5 and 6 represent the boundary of a special area of one mile radius around the Fulham Smallpox Hospital, London. The other circles represent zones of three-quarters of a mile, half a mile, and a quarter of a mile radius, respectively. The figures show the number of houses out of every hundred invaded by smallpox in the period between May 25th, 1884, and September 26th, 1885. The greater number of houses attacked in the quadrant lying southeast of the hospital may possibly be due to a greater prevalence of northwesterly winds during the period in question. The incidence of smallpox on every one hundred houses within the special area (a radius of one mile from the hospital) was 6.37. Within a quarter of a mile it was no less than 17.35, within a quarter and half a mile it was 9.25, within half and three-quarters of a mile it was 6.16, within three-quarters of a mile and a mile it fell to 2.57.

It is doubtful whether a smallpox patient is a source of infection in the period of incubation or even in the stage which precedes the eruption—the stage of invasion. There can be no doubt that the chief stages of infectivity are the earliest period of suppuration and the *Stadium Decrustationis* of Hebra, that is, the stage of desiccation or of drying up of the pustules, the *scabbing* stage.

Dr. William Heberden, in his "Commentaries on the History and Cure of Diseases" (London, 1803), says: "Many instances have occurred to me which show that one who has never had the smallpox may safely associate and even lie in the same bed with a variolous patient for the two or three first days of the eruption, without any danger of receiving the infection. One woman continued to suckle her infant for two days after the smallpox had begun to appear upon her, and the child being then removed escaped the distemper for that time, but was unquestionably capable of being infected, because he catched it about a year and a half after."

There is no relation between the severity of the type of the disease in the individual who is the source of the infection and in the individual who receives it. The lightest case may cause the most malignant, provided the susceptibility or predisposition of the victim who receives the infection is strong. On the other hand, the most severe confluent or malignant case may give rise to a very mild attack in a person whose susceptibility or predisposition is slight.

Sir Thomas Watson, in his classical "Lectures on the Practice of Medicine," mentions a remarkable instance of smallpox being caught from the dead body. The corpse of a man who had died of the dis-

ease was brought into Mr. Cæsar Hawkins' dissecting room in Windmill Street, London, with the result that four students took the disease, although only one had touched the body.

In a discussion on the mode of preventing the spread of epidemic disease from one country to another, in the Section of Preventive Medicine at the Seventh International Congress of Hygiene, London, 1891, Dr. Charles N. Hewitt, of Minnesota, recorded a still more striking case in which a female immigrant attended a smallpox patient on board ship while crossing the Atlantic from Liverpool to New York, then doffed and put by her clothes, which she again began to wear some time afterwards while attending a sick child in a distant part of the country, with the result that this child soon sickened of smallpox, the disease spreading until the fatal cases numbered one hundred. All the time the woman, whose clothes spread the disease, remained free from smallpox and perfectly well.

Dr. Wm. Osler,[18] of Baltimore, mentions what is perhaps in modern times the most remarkable instance of the rapid extension of the disease. Smallpox had been prevalent in Montreal between 1870 and 1875. It died out in the latter year, and the health reports show that the city was free from it until 1885. During the interval, vaccination, to which many of the French Canadians are opposed, was much neglected, so that a large unprotected population grew up. On February 28th, 1885, a Pullman car conductor, who had travelled from Chicago, where the disease was slightly prevalent, was admitted into the Hôtel-Dieu, Montreal, the civic smallpox hospital being at the time closed. Isolation was not carried out and on April 1st a servant in the hospital died of smallpox. After her death the hospital authorities, with deplorable want of judgment, dismissed all patients showing no signs of infection and who were able to go home. The malady spread like fire in dry grass, so that within nine months three thousand one hundred and sixty-four persons died of smallpox in Montreal, a city at that time of some two hundred thousand inhabitants.

Dr. Albert H. Buck[19] mentions a striking instance of the vitality of the poison of variola. In 1876 a child contracted smallpox in a house in New York. After the patient's recovery the carpets were removed, the walls were washed, and the room was carefully disinfected. New tenants shortly afterwards took possession of the room, and two years later (in 1878) a child was born. When two months old, being still unvaccinated, she became ill and soon presented all the features of well-developed smallpox. As the infant had never left the room and as at the time there was no smallpox in New York, but one inference was possible.

Clinical History and Symptomatology.

For convenience of description we may divide the course of smallpox into five stages: (1) Incubation, (2) invasion, (3) eruption, (4) secondary fever, (5) desiccation and desquamation.

Stage of Incubation.—This begins with the reception of the virus or poison of the disease into the system and ends at the appearance of the earliest symptoms. Its average duration is twelve days inclusive, except in cases of inoculation, when it is only eight days or even shorter. Curschmann declares that forty-eight hours only may elapse before the commencement of the phenomena resulting from inoculation. By this term is understood the engrafting of a disease by introducing its contagium directly into the body through puncture of the skin or by abrasion of a mucous membrane. A familiar example of the former method of inoculation is the every-day practice of vaccination. Inoculation through a mucous membrane has been practised from time immemorial in China, where the dried highly infectious smallpox crusts are sniffed up the nostrils like snuff.

I am indebted to Dr. John Marshall Day, resident medical officer of Cork Street Fever Hospital, Dublin, for notes of two recent cases, in which the length of the period of incubation was satisfactorily ascertained.

G. B——, a male aged 31 years, on the night of November 10th, 1892, slept at Preston, Lancashire, where variola was then prevalent. He crossed to Dublin the following day, but did not come into contact with any other source of infection. On November 18th he felt very ill, complaining of pains in the back, sore throat, shivering, and vomiting. On November 22d, a rash developed on his forehead. He was admitted to Cork Street Hospital on the 24th, suffering from discrete smallpox.

On Thursday, November 14th, the patient slept in his brother's bedroom and continued to do so until his admission to the hospital on the 24th. His brother fell ill on the night of Monday, the 5th of December, and in his case the rash of smallpox appeared on the morning of Saturday, December 10th. The facts here stated would support the view that variola is not very infectious until the rash appears. The incubation stage lasted nine or ten days (inclusive) in the first case, and could not have been less than eleven or twelve days in the second case.

Zuelzer[20] found the stage of incubation in hemorrhagic variola to be considerably shorter (six to eight days in nine cases) than in pustular variola.

As a rule there are no symptoms in this stage, but towards its close the patient probably feels unwell and out of sorts—what the

French aptly call *malaise*. Obermeier[21] has sometimes noticed in the last days of this stage a pharyngeal catarrh, with redness and swelling of the uvula and tonsils. This observation is of great interest. The lymphatic structures in the parts involved may be regarded as the first line of defence against a bacterial invasion. It is in the tonsils, and in those zones of lymphoid tissue which have been called the lingual and the pharyngeal tonsils, that the earliest encounters take place between the invading microbes and the defending leucocytes. The results will be local hyperæmia and possibly inflammation. In the present stage of our knowledge, however, this may, perhaps justly, be regarded as theoretical. The absence of symptoms gives to the stage of incubation the name of "latent period."

Stage of Invasion.—Smallpox sets in suddenly and with violence. As is usual in febrile disorders, the earliest symptoms are connected with the nervous system. They are chills or rigors, and in young children convulsions. The rigors vary from a mere feeling of chilliness to a downright shivering fit, with chattering teeth, pallor, blueness of the extremities, and "goose skin" (cutis anserina). More or less intense pain is complained of in the lumbar region or in the centre of the sacrum (rachialgia), apparently due to hyperæmia of the spinal cord, for it is almost invariably relieved by hemorrhage—natural or induced. Rheumatoid pains in the limbs are also often felt, so that the question of acute rheumatism has occasionally to be taken into account in the diagnosis (Hilton Fagge). Pain in the pit of the stomach is a tolerably constant symptom. It is often associated with, or accompanied by, nausea and vomiting, as well as constipation, except in children in whom diarrhœa may occur, together with sleepiness or drowsiness and stupor. Severe headache, giddiness (vertigo), often delirium and sometimes partial paraplegia, numbness of the extremities, retention or incontinence of urine, and incontinence of fæces are all symptoms of the profound influence of the poison upon the nervous system. So also is constant profuse sweating. There are, besides, loss of appetite (anorexia), thirst, furred tongue, very fetid breath, full and rapid pulse, and prostration. In women menstruation nearly always comes on, whether the monthly period is due or not, and it is generally profuse (menorrhagia).

All the foregoing symptoms are usually more acute and prolonged in confluent than in discrete smallpox, although it cannot be accepted as a general rule that the intensity of this initial stage bears a direct ratio to the severity of the whole attack. Violent prodromal nervous symptoms in sensitive individuals, such as women and children, may, and often do, usher in a mild attack of so-called varioloid. On the

other hand, when the initial symptoms are not severe, we may forecast a mild after-course of the disease.

On the first or second day the *temperature* rises to a considerable height, frequently to 104° F. (40° C.), seldom below this point, sometimes above it, even to 105.8° F. (41° C.). The maximal temperature (fastigium or acme of the fever) is usually reached shortly before the true rash of variola appears on the third day. This initial fever is commonly called the prodromal fever, because it runs before, or precedes, the appearance of the rash.

The *pulse* is full and tense in those who have been previously healthy. In severe cases it may be soft and dicrotic, as in typhoid fever (Curschmann). In rate, it is quickened in proportion to the temperature. It is influenced by age and sex, being very rapid (140–160) in young children, rapid in women (120–140), less rapid (108–120) in adult males.

The rate of *respiration* is quick, often out of proportion to the pulse and temperature. The breathing is short and labored, frequently amounting to dyspnœa and that without any perceptible or actual mischief in the breath organs. It is of the type called "cerebral respiration," which is probably induced by the brisk rise of body temperature and by the combined morbid influence on the respiratory centre of the variolous poison and of the superheated blood.

During the stage of invasion, or initial stage, *accidental rashes* are apt to appear, sometimes causing much difficulty in diagnosis. They are usually erythematous in character—if diffuse, resembling the blush of scarlatina or of erysipelas; if spotty, or macular, resembling measles or urticaria. Rayer[22] long ago gave to these prodromal rashes the name of *Roseola variolosa*, and it was adopted by Eimer[23] in 1853. Sir Samuel Wilks, Bart., president of the Royal College of Physicians of London, drew attention to these accidental rashes in Guy's Hospital Reports for 1857 and 1861.

These prodromal or initial erythematous rashes are very evanescent. They usually usher in an attack of varioloid or modified (mild) smallpox, and so have no little prognostic importance. They are not, however, pathognomonic, for they appear in other specific fevers as well as in variola—for instance, in typhoid fever and measles. This roseola variolosa probably depends on a reactive inhibition of the vasomotor system of nerves brought about by the fever poison. Hebra and Trousseau, as well as Curschmann, seem to have independently remarked that the parts affected by this form of erythema afterwards remain free from the proper smallpox rash. This observation has been generally confirmed by subsequent writers (Hilton Fagge and Pye Smith).

A more serious phenomenon is the development, even at this early stage, of petechiæ, or subcutaneous extravasations of dissolved hæmatin, varying in size from a pin's head to a pea or a bean. These purpuric rashes are commonly seen in the brachial and crural triangles of Th. Simon,[24] of Hamburg, the former embracing the lateral thoracic region, including the inner side of the arm, the armpit, and the pectoral region; the latter embracing the lower abdominal region, including the hypogastrium, the groins, and the inner aspect of the thighs. The prognosis in such cases is generally, but not necessarily, more grave.

Osler thinks that these initial rashes are more common in some epidemics than in others. They were certainly more frequent in the Montreal epidemics between 1870 and 1875 than they were in the more extensive outbreak in that city in 1885. According to Osler,[25] they occur in from ten to sixteen per cent. of the cases. Among his own patients in the smallpox department of the Montreal General Hospital the percentage was thirteen.

The duration of the stage of invasion is on the average three days; as a rule, it is prolonged in the milder, shortened in the severer cases. Sydenham,[26] speaking of confluent smallpox, observed: "This kind of smallpox generally comes out on the third day, sometimes earlier, but scarce ever later, whereas the *distinct* appears on the fourth day inclusive from the beginning of the distemper, or later, but very rarely before, and the sooner the pustules come out before the fourth day the more they run together." To the same effect Boerhaave wrote: "Most practitioners observe that the slower the smallpocks come out, the milder they prove and the better they ripen. Those appearing on the first day of the illness are esteemed the worst kind, those on the second, milder, those on the third, still more gentle, and on the fourth, the most favorable."

Trousseau and nearly all modern authorities concur in this view, but Curschmann thinks it is not warranted for all epidemics. It may, however, be accepted as a sound working proposition, although there is one striking exception to it. In consequence of some grave organic lesion—*ob atrocius aliquid symptoma*, as Sydenham writes—the outcoming of the rash may be delayed until the sixth or seventh day in both distinct and confluent cases—*malo semper omine.* Trousseau[27] illustrated this by the case of a woman, aged thirty, in whom the rash did not appear until the fifth day. At the beginning of her attack of smallpox she had all the symptoms of sporadic cholera: vomiting, purging, cramps, general coldness of the surface, blanching of the mucous membranes, dry cold tongue, injection of the conjunctivæ, and a dull appearance of the corneæ. The choleraic

symptoms ceased on the fourth day, and on the fifth the rash of smallpox appeared.

A long experience in the wards of Cork Street Fever Hospital, Dublin, has led me to the conclusion that a purpuric or hemorrhagic tendency early in smallpox also postpones—it may be indefinitely—the appearance of the true variolous exanthem. To this subject it will be necessary to return.

Before leaving the initial stage, or stage of invasion, it should be stated that in rare instances an attack of smallpox may terminate with this stage, no true eruption following it. Such an attack may well be called *Variola sine exanthemate*, or *Variola sine variolis*. The symptoms are those of the invasion stage—chills, followed by fever of varying severity, prostration, headache, backache, nausea, vomiting, constipation, and sore throat; often an erythematous or petechial rash, especially affecting the crural triangles. After a few days, the temperature falls fast and the patient gets well.

This mild form of smallpox was well known to Sydenham and the older writers like de Haen, John Peter Frank, and others. Sydenham named it with much propriety *Febris variolosa*—to this the words "*sine exanthemate*" were subsequently added. In proof of the existence of a *variola sine variolis*, Curschmann recalls the oft-mentioned though rare cases which have occurred in pregnancy, when the birth of a child covered with a smallpox eruption has at times revealed the nature of the previously doubtful nature of the mother's attack.

Stage of Eruption.—The true exanthem, or rash, of smallpox appears first on the forehead, neck, and face, and about the wrists, next on the trunk, lastly on the lower extremities. ("Genæ, labia, collum, stigmata gerere prima solent, pectus deinde, dorsum ac venter, tandem et artus."—Antonius de Haen, "Ratio Medendi," Tomus secundus, p. 54, Viennæ, Austriæ, 1774.) In severe cases, as has been already stated, it shows itself on the second or even on the first day; in mild cases its coming may be postponed until the fourth day. ("In Discretis Variolis die ab invasione quarto prodire hæc Stigmata solent; in Confluentibus die tertio, imo et finito necdum secundo."—Antonius de Haen, *loc. cit.*) The usual time for its appearance is the *third day, inclusive*, from the earliest symptoms. It is alleged that with the aid of photography the presence of a smallpox rash in the skin can be detected several hours before it reveals itself to the eye. All writers agree that the rash is most copious on the most vascular parts of the surface, for example the face. Temporary hyperæmia caused by wounds leads to an excessive development of the rash. Trousseau mentioned the case of a lad in whom the eruption was

very abundant on the posterior aspect of the forearms. He was a cook, and in that capacity had these parts constantly exposed to the heat of kitchen stoves.

When the "pocks" fulfil their life history, they are seen to pass through the following phases of development:

1. *Specks of hyperæmia*, or *macules*, like the fine pricks made with a needle, and sometimes like recent flea-bites (first day of rash).

2. *Papules* or *pimples* quickly form, owing to changes in the rete mucosum of the skin and to cell proliferation. These papules are like those which are met with in persons affected with lichen or prurigo (Trousseau). They are at first slightly raised, then conical, already hard or "shotty" to the touch, feeling like grains of shot beneath the skin (second and third days of the rash).

3. *Vesicles.* Exudation of serum soon takes place, so that the horny layer of the epidermis is raised to form a vesicle. This is at first filled with a clear, transparent, somewhat viscid fluid, which quickly becomes opaque, lactescent, or milk-like (fourth and fifth days of the rash). "By the fourth or fifth day of the eruption (seventh or eighth of the disease)," writes Dr. Hilton Fagge, "the vesicle is generally as large as a split pea, hemispherical in form and opaline in appearance."

4. *Pustules*, or small abscesses, are next formed by a further change in the contents of the vesicles, in which young cells increase and multiply, causing them to assume a more and more opaque and yellow appearance and to increase quickly in size. The contents are now purulent (sixth and seventh days of the rash). About this time also a central depression or *dimple* (German, *Pocken-nabel*) is found in these pustules. This is the so-called umbilicus, at the bottom of which the opening of a hair follicle or sweat gland is frequently seen, according to Curschmann. This is thought by Unna to be a mere coincidence and devoid of etiological significance. The variolous inflammation is not confined to the epidermis. The papillary layer of the derma is often involved, its connective-tissue elements proliferate and afterwards undergo cicatricial contraction, leading to the permanent deformity known as "pitting." A person is then said to be "pock-marked" (French, *picoté*).

The period of fullest development of the rash is reached on the seventh day from its appearance—that is to say, the tenth day, inclusive, of the disease. The pustule, when at its height, is often quite hemispherical, the umbilication having disappeared. These pustules are really small abscesses. They become extremely painful, and the pain is accompanied by great swelling of the affected parts—greatest where the tissues are loosest or most relaxed, as in the eyelids and

lips, and about the prepuce. In the confluent variety, about to be described, the face swells to a shapeless mass, rendering the patient absolutely unrecognizable.

When fully developed, each pustule is surrounded with an inflammatory zone or areola, called its "halo."

The period of fullest development of the rash is called the period

Fig. 7.—Confluent Smallpox. Pustular stage on body ; crusting stage on face.

of maturation or ripening. It lasts about three days and is followed by the last stage in the life history of the eruption, that of—

5. *Desiccation*, or the rupture and drying up of the pustules and the formation of *crusts* or *scabs*, which in the severer cases exhale a pungent and abominably fetid odor.

The appearances presented by the rash in its pustular and desiccation stages are shown in Figs. 7, 8, and 9. The original photographs were taken by one of my pupils, Mr. John Prescott, during the last epidemic in Dublin. The three patients were all members of the same family. All the patients happily recovered.

Stage of Desiccation.—Even before the eleventh day the pustules

in many instances burst, either from overdistention or by accident, and in other instances a thick, viscid, yellowish matter—in appearance and consistence not unlike honey—oozes from the as yet unbroken surface. This sticky exudation exhales the overpowering smell just referred to. Together with the other contents of the pustules, the foul exudation speedily dries up, first in the centre, as represented in Fig. 7. Brownish scabs are in this way formed, which are at first adherent but afterwards fall off in from three to six days, leaving elevations or projections of a violet-red hue, like a cold skin. It should be mentioned that the pustules do not pass through their sev-

Fig. 8.—Confluent Smallpox. Commencing desiccation.

eral stages simultaneously, and further that in some cases they dry up through absorption of their contents without bursting.

On the trunk and extremities, where desiccation begins later than on the face, the pustules frequently burst and their purulent contents soaking into the bedclothes and body linen, undergo rapid decomposition upon the skin and in the clothing, causing an overwhelming stench about the eleventh or twelfth day of the disease. This occurs in the confluent, not in the discrete, form. With the drying up of the pustules, the redness, swelling, and tenderness of the skin subside, the eyes reopen, the nostrils are cleared, and the features of the patient become once more recognizable. The separation of the crusts may take place very slowly in severe and confluent cases, extending over many weeks.

Stage of Desquamation.—When the scabs have fallen off, successive scales of epidermis form and peel off, a process which is called

desquamation or shedding of the skin. Should the variolous inflammation (dermatitis) have dipped deep and involved the papillary layer, or *cutis vera*, a small, white, puckered scar or "pit" (cicatrix) is ultimately left, and the person is said to be "pock-marked." In severe cases the deformity is extreme and permanent, in other in-

FIG. 9.—Confluent Smallpox. Separation of crusts, showing pitting.

stances time smoothes the puckered surface, and the *pitting* shows only in cold weather, when the muscular fibres of the skin are rigidly contracted. The pock-marked skin is more or less anæmic, owing to the constriction or even obliteration of the arterioles which carry the blood to it. Persistent baldness may result from confluent smallpox. When every scab has fallen off and the process of desquamation has ceased, the patient may be looked upon as free from infection.

The stage of desquamation, or scaling, sets in after the eighteenth

day or so of an attack of confluent smallpox. In discrete cases it sets in earlier but is not so well marked and is branny rather than flaky in character—that is, the individual particles of shed cuticle are small, like fragments of bran (furfuraceous desquamation, from the Latin, *furfur*, bran).

The true rash of smallpox is by no means confined to the skin. About the same time that the rash shows externally, it develops on the mucous membranes also. Of this we have ocular proof in the case of those tracts of mucous membrane which are visible and are most exposed to the air. Thus, the conjunctivæ, the mucous membranes of the nose, mouth, pharynx, and adjacent parts, are nearly always affected. The rash may thence extend through the whole system of mucous membranes, invading the larynx, trachea, and bronchi in one direction; the œsophagus, stomach, and intestines in another. Thence arise many of the more serious complications of smallpox. The eyes and eyelids are inflamed and sight may be lost. We may have deafness, due to blocking of the œdematous Eustachian tubes (Wendt[28]); hoarseness and aphonia with acute œdema of the glottis; cough and dyspnœa, from bronchitis and pneumonia; dysphagia, or difficulty of swallowing; diarrhœa; colitis and dysenteric stools.

It is true that Curschmann states that it is very doubtful if real pustules are ever formed in the stomach and intestines, although they have been described by the older writers, for example by Robert in his account of an epidemic in Marseilles. He adds that they are seen only in the lowest part of the rectum, close to the anus. Curschmann adds that real pustules or diphtheritic inflammation may occur in the vulva and vagina, but that pustules are never found in the urinary bladder or in the urethra except close to the meatus. In illustration of the distribution of the variolous eruption upon the mucous membranes, I have for many years had an opportunity of exhibiting to my classes on Practice of Medicine at the Royal College of Surgeons in Ireland a series of beautiful original drawings by the late Mr. John Conolly, of Dublin. These drawings of the pathological appearances in smallpox show the entire respiratory and digestive tracts thickly beset with a variolous eruption, presenting itself as a number of whitish or pearly-gray ulcerations upon a reddened base, with abrasions or large and irregular excoriations of the mucous membranes. Only upon such mucous membranes as are exposed to the external air are fully developed pustules to be seen—a fact which would point to a secondary bacterial infection by the Streptococcus pyogenes as the determining cause of pustulation.

Dr. Meredith Richards, medical officer of health for Chesterfield,

calls attention[29] to post-eruptive rashes in smallpox. These include: 1. A scarlatiniform erythema, general in distribution and not differing from that which is so common in various septic states; 2. A development of the pustules which appears to correspond to Radcliffe Crocker's *Impetigo contagiosa gyrata* (*British Medical Journal*, Vol. II., 1895, page 1102); 3. A development of the previously healthy interpustular epidermis into flaccid bullæ, containing a few drops of foul mucopurulent fluid. These bullæ are soon followed by profuse desquamation which may lead to the shedding of the nails, and are accompanied by severe constitutional symptoms of a septicæmic character.

In the second variety the smallpox pustules, instead of drying up and scabbing on the eleventh day, show signs of spreading peripherally, so that in a day or two many of the cutaneous lesions consist of three well-defined parts, namely, a central scab, a surrounding vesicular ring which rapidly becomes pustular, and a red areola surrounding the pustular ring. Unless treated, the areola and pustular ring continue to spread centrifugally until the whole lesion may measure an inch or more in diameter. This rash is clinically important because it is often attended by high temperature and other signs of septicæmia.

A secondary infection by various pyogenic microorganisms, especially Staphylococcus pyogenes aureus and Streptococcus pyogenes, is doubtless the cause of these lesions. To such a secondary infection the terms "staphylococcia" and "staphylostreptococcia" have been applied. The condition is not peculiar to smallpox, but has been observed in chickenpox as well by Hulot, Hutinel, Labbé, and others. Recently Pirro Bolognini[30] has described a series of cases of varicellous staphylococcia.

According to Curschmann, true pocks upon serous membranes are fables belonging to antiquity. Very striking morbid appearances are, however, presented by serous membranes in the malignant and purpuric forms of variola. Thus, the pleura, the pericardium, and the peritoneum may be the seat of blood extravasations varying in size from mere pin points (petechiæ) to large ecchymoses.

A *classification* of smallpox based upon the distribution and amount of the rash has been handed down from the time of Sydenham, the father of English medicine, as he has been well called. Such a classification has received universal acceptance and must therefore be described at some length.

Under all circumstances—whether modified by a previous attack or by vaccination, or unmodified—smallpox appears under two principal forms—discrete or distinct, and confluent. The first of these

varieties of the disease is commonly free from danger; the latter is one of the most terrible, loathsome, and fatal of maladies. Of confluent smallpox two modified varieties are recognized, namely: (1) semiconfluent or coherent smallpox, and (2) corymbose or clustered smallpox.

Variola discreta vel distincta is the name given to those cases in which the rash comes out late, is sparse or scanty, fails in many instances to run through its whole course, aborting as it were in the papular or vesicular stage, and causes comparatively slight secondary inflammation of the skin. In this relatively mild form the several papules, or pustules—if they form at all—are studded over the skin, being more or less widely separated from each other; hence the term discrete (from Latin, *discerno*, I separate). In this form the initial symptoms may be, but are by no means necessarily or even generally, less acute than in variola confluens. The symptoms, however, usually subside quickly—they are less persistent. When the rash stops short of the pustular stage, as not infrequently happens, the name *Variola crystallina* is given to the case. When not even vesicles are formed, the attack is described as one of *Variola cornea* or *hornpox*. In vesicular smallpox the contents of the vesicles may be rapidly absorbed and the vesicles then shrivel and dry up, constituting the so-called *Variola verrucosa* or *wartpox*.

Discrete smallpox may be mistaken for chickenpox, or chickenpox for it; but regard to the severity of the constitutional symptoms in smallpox should guard one against making so serious a mistake.

Variola confluens is the term applied to those cases in which the true rash overruns the whole, or nearly the whole, surface of the body, and invades the mucous membranes also with great severity. The symptoms of the invasion stage are all intensified, and the rash appears as early as the second day. The secondary inflammation of the skin is extreme, and ulcerative processes are apt to cause great losses of substance and permanent scarring and disfigurement. On the scalp the hair follicles may be destroyed to a greater or less extent, leading to complete or partial permanent alopecia or baldness.

As additional and very characteristic symptoms in this dangerous variety of the disease, Trousseau mentions: (1) Persistent diarrhœa, both in adults and in children; (2) profuse salivation in adults, resulting either from secondary parotitis, or as a reflex symptom from inflammation of the mucous membranes of the mouth, stomatitis (Curschmann); (3) great tumefaction of the face and eyelids, so that the latter sometimes burst or slough; and (4) most painful swelling of the hands and feet. This last symptom is well shown, so far as the hands are concerned, in Figs. 7 and 8. Salivation, or

ptyalism, sets in early and is extraordinarily profuse. According to Trousseau, from one to two litres (that is, from thirty-five to seventy fluidounces) of clear, but ropy or viscid, saliva may flow from the patient's mouth within twenty-four hours, and this ptyalism is accompanied by a burning, unquenchable thirst.

To omit special mention of the delirium of confluent smallpox would be very misleading. In the epidemics of 1871 and 1878 in Cork Street Hospital, Dublin, the occurrence of delirium was one of the commonest and most striking features of the malady. It was often violent and noisy (delirium ferox), or "busy" with extreme muscular agitation (delirium tremens). In the later stages of the attack, when the vital and mental powers were swooning, it assumed more of the low muttering type (the "typhomania" of Galen). Both at the Meath Hospital and at Cork Street Hospital, attempts at suicide were made by delirious smallpox patients, and homicide has happened before now as the outcome of delirium ferox, the raving and frenzy of the condition making a dangerous maniac of the unhappy patient for the time being. Huxham, in his "Essay on Fevers," graphically describes the rash in these cases as consisting of pocks which are "pale, crude, pitted, and *sessile.*"

The face is covered with pustules, which run together so that the epidermis is raised by a milky seropurulent secretion, and the face seems as if it were dipped in tallow or covered with a mask of parchment—"*Pergamenæ speciem visu horrendam* (*cutis faciei*) *exhibit,*" as Morton said in his "Pyretologia." It is right to mention that in confluent smallpox, while the face and hands may be absolutely covered with pocks, in other parts of the body the eruption may be more or less discrete, the amount and intensity of the pustulation seemingly bearing a direct relation to the vascularity and inflammatory state of the surface. This was pointed out many years ago in an admirable paper on the "Treatment of Smallpox" by the late Dr. William Stokes.[31] Of this fact we have two direct proofs. In the first place, portions of skin which have been subjected to mechanical or chemical irritation, either before infection or during the stage of incubation, invariably throw out a very abundant pustular, frequently a confluent, eruption even in discrete cases of smallpox. Secondly, and conversely, where the vascularity of a part has been reduced by pressure, local depletion, or removal of irritation by poulticing, fomenting, bathing, or other means, the eruption of smallpox remains distinct even in confluent cases.[31]

The mucous membranes, like the skin, are the seat of a closely set rash in confluent smallpox, and very dangerous forms of secondary inflammation are apt to place the patient's life in imminent peril.

Glossitis variolosa, or diffuse inflammation of the tongue; diphtheria, acute œdema of the glottis, intense and widespread bronchitis, and pneumonia; violent, uncontrollable vomiting, retching, and diarrhœa, are among the evidences we have of the serious engagement of the mucous membranes. Towards the close, should the patient survive, multiple pyæmic abscesses, erysipelas, and even gangrene may occur in those parts of the integument where the confluence is most pronounced. The mortality is, of course, very great in this form of the disease, at any stage of which the patient may succumb. In some epidemics, according to Trousseau, half the patients die; in others, four-fifths, and in others, less fatal, one-third of those attacked perish. Confluent smallpox is, therefore, the most deadly of all pestilences, yellow fever, bubonic plague, and cholera not excepted. The terrible feature about smallpox is that it may kill not only in the acute stage, by inducing dissolution of the blood or by the intensity of the fever, but also in the later stages and in convalescence. The most fatal epoch is about the eleventh or twelfth day, but even far on in the stage of desiccation death not infrequently results from exhaustion, or pyæmia, or some other complication. It will be necessary to return to the subject of mortality later on. Should confluent smallpox end in recovery, convalescence is apt to be very tedious, and is frequently interrupted by serious sequelæ, of which an "acute furuncular diathesis," as Trousseau calls it, is one of the commonest and most troublesome. It shows itself in the formation of successive crops of most painful boils and of more or less deep-seated abscesses. This acute furunculosis is doubtless due to secondary infections by the various pus cocci, especially Staphylococcus pyogenes aureus, but also Staphylococcus pyogenes albus and Streptococcus pyogenes, the last being the micrococcus of erysipelas described by Fehleisen. As Sternberg[32] puts it: "In man the ever-present pus cocci are more likely to invade the tissues, forming furuncles, carbuncles, and pustular skin eruptions, or erysipelatous and phlegmonous inflammations, when the standard of health is reduced from any cause, and especially when by absorption or retention various toxic organic products are present in the body in excess. It is thus that we would explain the liability to these local infections, as complications or sequelæ of various specific infectious diseases."

In the stage of desiccation large ecthymoid crusts form upon the ulcerated surface of the skin. These become detached, leaving the dermis scooped out. Successive layers of thinner and thinner crusts form, and are shed through two, three, or four weeks, the ulcerations finally cicatrizing, leaving the rugged scars which seam the faces of those who have passed through confluent smallpox. To this dis-

figurement the term "pitting" has been applied, and (as has been already stated) the person affected is said to be "pock-marked." Pitting is especially unsightly about the nose, the borders of the alæ nasi appearing indented and the bridge and tip of the nose split and torn. Dr. John MacCombie[33] describes a *verrucose* or warty condition of the skin of the nose and cheeks as resulting not infrequently from deep ulceration. In a few confluent cases in which there is deep ulceration with much dermatitis, bands of cicatricial tissue form, and a *cheloid* condition results. The face, which is the part most usually affected, becomes scarred and disfigured; ectropion and distortion of the mouth may result.

With the separation of the scabs, or sometimes later, the hair commonly falls off, in some cases in handfuls. If the variolous inflammation of the scalp has dipped deeply and involved the hair follicles to any great extent, the resulting alopecia may be permanent. More usually the hair grows again, in a few cases more luxuriantly, if less smoothly, than before. It is not usual for the nails to fall off after smallpox, although the atrophic furrows across them, described and figured by A. Vogel and mentioned by Murchison[34] as occurring in typhus fever, are not infrequently observed.

It has been already stated that two modifications of confluent smallpox are recognized as regards the distribution of the rash. These are the semiconfluent and the corymbose varieties.

The term *Variola semiconfluens*, or coherent smallpox, is applied to those cases (1) in which the pustules touch one another without coalescing, or (2) in which the eruption is confluent on and about the face, but more or less discrete elsewhere.

Mr. Marson, formerly of the London Smallpox Hospital, first applied the term *variola corymbosa* to those cases in which the pustules are confluent in patches or clusters (hence the name *corymbose*, from κόρυμβος, a cluster of fruit) these have been separated from each other by intervals of unaffected skin. Vascular parts, like the armpits, groins, and popliteal spaces, are often the seat of a rash of this kind.

Hilton Fagge says that he never saw an example of corymbose smallpox, but there is a beautiful drawing of it in the collection of John Conolly's illustrations of smallpox observed in the Hardwicke Fever Hospital, Dublin, to which allusion has already been made. According to Marson, this is a very fatal variety of the disease, the mortality reaching forty-one per cent. Strangely enough, in the London Smallpox Hospital it was scarcely less destructive to vaccinated individuals than to those who were unprotected (Hilton Fagge).

Varieties.

Apart from the classical and recognized forms of discrete and confluent smallpox, we meet also with the following varieties of the malady:

1. *Variola benigna* (*Varioloid*—French, *variole modifiée*). This is a mild and abortive form of smallpox in which the pocks either fail to appear at all (*Variola sine exanthemate*, or *V. sine variolis*), or else fail to pass through the later stages of their development, stopping short at the papular stage (*Variola cornea*, or "hornpox"), or, if reaching the vesicular stage, drying up and shrivelling on the fifth or sixth day of the eruption (*Variola verrucosa*, or "wartpox"). In other instances the exanthem passes rapidly and imperfectly through all phases of its development, producing more or less dwarfed forms of the pustules.

Some readers may be sceptical as to the existence of a Variola sine variolis, but the evidence is overwhelming that there really is such a form of smallpox. After a well-marked initial stage, the attack aborts and the patient is well again in three, four, or six days at the latest. Dr. Hilton Fagge refers to one instance of the kind, which was attended by a characteristic roseola, with the exception of which there was no reason to suspect smallpox. Simon has recorded a similar case, in which the disease aborted, notwithstanding that its real nature was proved by the patient's sister suffering from an attack of variola at the same time. Another example of it is thus described by Marson. A lady walked with a person already affected with smallpox. Twelve days afterwards she was taken ill; she was for a few hours delirious, but her illness passed off without eruption. Twelve days later still, her sister, who had not been out of the house for three months, was attacked with the same disease, which in her case ultimately assumed a confluent form. Curschmann mentions the case of a woman who was seized with shivering, fever, headache, and pain in the back, so that, as variola was epidemic at the time, she seemed without doubt to be passing through the initial stage of that disease. On the fourth day defervescence occurred, no rash could be detected, and by the tenth day she felt and was perfectly well. However, she gave birth to an infant which was covered with an early eruption of smallpox. This afterwards suppurated and proved fatal.

In the case of the so-called wartpox the solid part of the pock remains for a long time, presenting the appearance of a wart, hence the name "wartpox" (Latin, *verruca*, a wart).

Curschmann aptly points out that "varioloid" is nothing more

than a form of true smallpox with a milder course and a shorter duration. Many individuals are attacked only by this form because of a naturally slight susceptibility to the contagium of the disease. Again, when the immunity gained through a previous attack of smallpox, or from a previous inoculation, or by vaccination, has become impaired through lapse of time, then exposure to the poison may induce an attack of modified smallpox or varioloid. There can be no doubt that this mild form of so dreadful a disease as variola commonly is has become relatively much more frequent since vaccination was introduced about a century ago.

As stated above, Hebra, Trousseau, and Curschmann all consider that, as a rule, the development of the pocks is less the more extensive is the initial erythematous eruption. Viewed in this light the purely erythematous rashes of the invasion stage come to be of decided value in prognosis. It has been already explained that these rashes are to be carefully distinguished from the petechiæ which form in the earliest stage of some cases of the terrible purpuric or hemorrhagic smallpox which will be now described.

Variola Maligna, Variola Purpurica vel Hæmorrhagica.—Observations of some three thousand cases of smallpox in two hospitals and during two epidemics have led the writer to the conclusion that apart from confluent smallpox, in which the patient's life is endangered by the amount of suppuration and the intensity of the secondary or suppurative fever—the so-called "fever of maturation"—malignant smallpox presents itself clinically under two forms: (1) purpuric and (2) hemorrhagic. These forms differ merely in degree; in both the blood is profoundly altered and devitalized to such an extent that it is apparently rendered incapable of throwing out or developing the characteristic or pathognomonic rash of variola. In the purpuric variety the "dissolution of the blood," as it has been called by the older writers, leads to the formation of petechiæ, vibices, or purple streaks or blotches, and ecchymoses—appearances connected with the skin which are sufficiently well known as the outcome of blood changes in the graver forms of most infective diseases such as smallpox, typhus, scarlatina, measles, and others. According to this view, the blood is so devitalized and defibrinated as to establish an acute *hæmatophilia*, the patients becoming "bleeders" from an infective dissolution of the blood or *hæmatolysis*. Murchison, adopting this view, defines the dark purple or bluish points in the skin, to which the name of true *petechiæ* is applied, as consisting of an infiltration of dissolved hæmatin into the tissue of the cutis. The bruise-like swellings (*vibices*) are caused by hemorrhage into the subcutaneous and intermuscular connective tissues (John MacCombie).

Here it is right to state that so competent an authority as Unna, of Hamburg, maintains that the doctrine of "blood dissolution" in infective diseases is obsolete. With Klebs he connects the cutaneous hemorrhages of these diseases with blocking of the vessels of the skin by bacteria. The infective forms of purpura are, according to Unna, most simply explained in this way, and he thinks that the theory of bacterial coagulation-thrombosis will probably play an important rôle in morbid anatomy in the not distant future. In an article on typhus fever the writer[35] pointed out that, applying this view to typhus, the petechiæ which constitute the later stage of the eruption of that disease would be the result of a diapedesis, depending in its turn on clotting of plasma and consecutive stagnation round bacterial emboli. This view, *mutatis mutandis*, is equally applicable to smallpox and to typhus.

In hemorrhagic smallpox, the "dissolution of the blood," or the bacterial coagulation-thrombosis, according to the theory we adopt, is carried still further than in purpuric smallpox. A condition of acute hæmatophilia is in fact produced, so that the ill-fated sufferer bleeds from every pore and orifice of the body. There is chemosis, blood being effused into the connective tissue binding the conjunctiva to the eyeball, sometimes to the point of bursting so that the patient may even weep tears of blood. Retinal hemorrhage may destroy eyesight. There is epistaxis—terrible because uncontrollable. Blood oozes from the lips and gums. The patient spits or coughs up blood, he vomits blood. The motions from the bowels are tarry. Blood pours from the kidneys, and in the female from the genital organs. The tongue looks as if it was parboiled, and there is an unquenchable thirst. Under these circumstances, unless the hemorrhage is stanched by turpentine and ergot, or ferric chloride, or pyrogallic, gallic, or tannic acids, or other means, death speedily ensues—too often, alas, even in spite of all that human skill and care and devotion can do.

One of the most extraordinary as well as the most painful features of this deadly malady is the clearness of mind which often remains with the unhappy patient almost up to the time when he draws his latest breath. There is in some instances no delirium, no stupor, no dulling of the intellect whatever—the victim literally looks death in the face in full possession of his senses. It has happened to me to be asked by a patient at 11 A.M. how long he had to live, and that patient lay dead four hours afterwards. As Curschmann quaintly says, "only a few patients are fortunate enough to fall speedily into delirium or coma."

The cessation of the bleeding may bring back hemorrhagic small-

pox to the purpuric form, and in the case of the latter variety of malignant smallpox the restoration of the blood, evidenced by the brightening of the purpuric spots, may be followed by the tardy development of a copious eruption of either aborted pustules (papules), in which case the patient happily makes a speedy recovery, and that too without suffering from a fever of maturation, or true and fully formed pustules, when the patient has still to run the gauntlet of a severe attack of confluent smallpox, with its secondary fever, complications, and sequelæ. This is the idea of malignant smallpox which the writer has formed from a lengthened experience.

Strong muscular men, the young and robust, and pregnant or recently delivered women are said to be particularly liable to fatal hemorrhagic smallpox, and this was certainly the case in the Dublin epidemics of 1871, 1878, and 1894–95. Curschmann, agreeing in this view, adds that he has often met with this grave variety of the disease also in delicate persons and in drunkards. Marson expressed the opinion years ago that the blood, in this form of smallpox "is poisoned from the very first and is rendered very fluid and watery."

In the fact that the true eruption does not develop, the two extremes of smallpox as regards gravity meet, the most benignant form, described by Sydenham, Peter Frank, and others as *Febris variolosa sine exanthemate*—what de Haen called *Variolæ sine variolis*—and the so-called *Purpura variolosa*, the most malignant form leading, as we have seen, to almost certain death. Under this latter title Curschmann includes those cases in which the process designated "hemorrhagic diathesis," but which the writer prefers to call "acute hæmatophilia," imprints its frightful stamp upon the disease even in its initial stage, or during the eruptive stage, or at the close of the latter.

Variola Hæmorrhagica Pustulosa.—We have just stated that hemorrhagic or purpuric symptoms may occur not only in the stage of invasion (when they constitute ordinary purpuric or hemorrhagic smallpox—*Purpura variolosa*), but also at almost any time in the stage of eruption. In order to distinguish these latter cases, as a matter of convenience Curschmann employs the term Variola hæmorrhagica pustulosa. In this form of purpuric smallpox, the true exanthem may become the seat of hemorrhage in the papular, the vesicular, or the pustular stage; most commonly the pocks are about the size of a lentil when the bleeding into them begins, and the characteristic appearance is seen first on the lower extremities.

This variety of smallpox corresponds exactly to the "anomalous" or "irregular" smallpox of 1670, so described by Sydenham, who also speaks of the malady as "this dangerous *black smallpox*" (*Variolæ nigræ*), in which "the eruptions were more inflamed, and in the

declension after their suppuration frequently looked black." Another name for this variety is *Variolæ cruentæ* (bloody smallpox).

From the foregoing description we may compile a table of the varieties of smallpox, which will prove useful for reference. It will be observed that variola discreta finds a place in both portions of the table.

I. *Variola Vera—Natural Smallpox.*

1. *Variola discreta*, vel *distincta.*
2. *Variola confluens—*
   (1) *V. semiconfluens* (coherent smallpox).
   (2) *V. corymbosa.*
3. *Variola maligna—*
   (1) *V. purpurica.* } *Variolæ nigræ.*
   (2) *V. hæmorrhagica.* }
   (3) *V. hæmorrhagica pustulosa* (Curschmann) (Syn.: *Variolæ nigræ*, vel *cruentæ*).

II. *Variola modificata*, vel *mitigata—Varioloid; (Variole Modifiée)—Modified Smallpox.*

1. *Variola benigna—*
   (1) *V. sine variolis* (variolous fever).
   (2) *V. cornea*, vel *verrucosa* (hornpox, or wartpox).
   (3) *V. discreta*, vel *distincta.*

In drawing attention to this table I wish emphatically to enforce the view that all these various forms are merely modifications of one and the same disease, namely, *smallpox.* We classify these varieties simply as a matter of convenience, and with Curschmann we should hold that "none of these forms are sharply defined amidst the great group of variolous affections; but there is rather a gradual transition from one into the other, so that general outlines are to be associated with the most customary designations rather than sharply circumscribed features" (Curschmann[5]).

Temperature.

As pointed out by Wunderlich,[36] the fever in variola exhibits two distinct types, which closely correspond, however, at their commencement. One of these types is a brief *continuous* fever belonging in particular to the milder forms of variola discreta and to most cases of varioloid or modified smallpox, occurring chiefly, although not exclusively, in vaccinated or inoculated persons. This is the so-called *prodromal* or *initial fever* of the stage of invasion. In the forms of

the disease just mentioned, this continuous fever both begins and usually completes the febrile movement. The *maximal* temperature of the initial or prodromal fever is rarely less than 104° F. (40° C.); it generally exceeds this, reaching even 106° F. (41.1° C.). This great height is quickly attained, generally on the second day. Soon after the true rash of smallpox appears the temperature falls more or less rapidly, usually from the fourth to the sixth day. The defervescence is either rapid and continuous, or slower and interrupted by a moderate evening exacerbation. In cases of uncomplicated varioloid and of mild discrete smallpox this defervescence is complete and final.

The fall of temperature which occurs with the coming out of the rash of smallpox is pathognomonic of this disease, and is therefore of the first importance in diagnosis. It is exactly the converse of the behavior of the temperature in measles, in which the fever is moderate up to the appearance of the rash and then becomes more and more intense until the rash is most fully developed. It should be borne in mind that the initial or prodromal fever is often very severe even in the mildest cases.

The other type of fever in smallpox is a *relapsing* type, which is characteristic of true smallpox in its severer and confluent forms. The falling temperature after the prodromal stage in this case either never reaches the normal line, remaining at subfebrile (99.5°–100.4° F.) or even at febrile points (100.4°–102.2° F. in the morning, rising to 103° F. in the evening); or the normal temperature is reached, if at all, tediously and defervescence is by lysis.

Then, with the beginning of pustulation, or ripening (maturation), of the exanthem, the temperature again begins to rise, ushering in a *secondary* fever—the *fever of suppuration* or of *maturation* as it is called ("Eiterungsfieber" of the Germans), which is of indefinite duration and varies in intensity according to the severity of the disease. In a sharp attack of discrete or semiconfluent smallpox, the temperature in this secondary fever rarely exceeds 103° or 104° F.; there are morning remissions, and the duration is only a few days. In bad confluent smallpox, on the other hand, the fever runs very high, presenting sometimes a remittent course with marked exacerbations, sometimes a continuous range with occasional isolated elevations or *spikings* of temperature.

Repeated elevations of temperature above 104° F. (40° C.) during this fever of suppuration, or maturation, are a sign of great danger. In cases which tend towards recovery, defervescence takes place by an irregular lysis. In fatal cases, *hyperpyrexial temperatures* (107.6° F.=42° C.) are wont to occur before, at the moment of, or even after death. Th. Simon,[37] of Hamburg, has published two cases in which

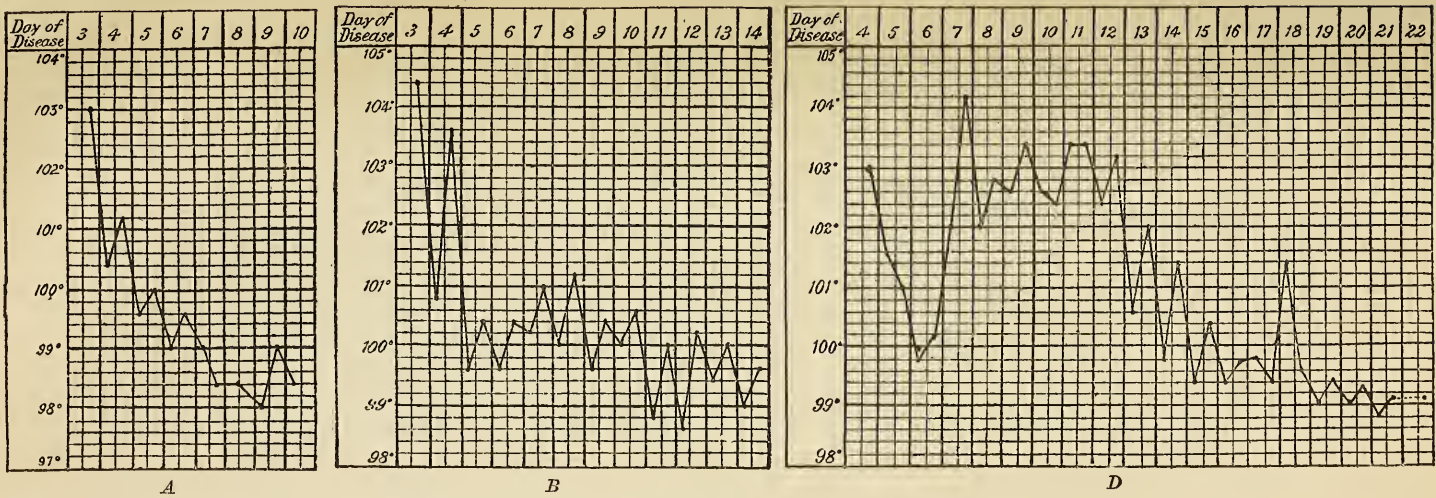

FIG. 10.—Charts Showing the Temperature Range in Smallpox. *A*, Variola discreta, with no secondary fever; *B*, variola discreta, with slight secondary fever; *C*, variola cohærens, with marked secondary fever; *D*, variola confluens, with severe secondary fever; *E*, variola confluens, with intense secondary fever.

the temperatures after death were 110.75° and 112.1° F. respectively. In Plate IV. illustrating his work on "Medical Thermometry," Wunderlich includes a chart of the temperature in a case of smallpox, fatal in the suppurating stage, in which the thermometer marked 109.2° F. shortly before death.

The accompanying temperature charts (Fig. 10) are from cases observed by me in the wards of Cork Street Fever Hospital, Dublin, and the Meath Hospital and County Dublin Infirmary.

Complications and Sequelæ.

The complications and sequelæ of smallpox are many and severe. They arise either from the direct effects of the fever poison and its products on different parts of the body or from some secondary and accidental infection by other pathogenic organisms than those peculiar to smallpox. It will be necessary to enumerate these in detail.

1. *The Skin.*—As the brunt of variolous poisoning in most cases falls upon the skin, it is to be expected that it should suffer severely. We therefore are not surprised to find that the skin may be the seat of *multiple abscesses*. These vary in size from a pea to a child's head. They make their appearance in and after the scabbing stage and may indefinitely protract convalescence. At Cork Street Fever Hospital, Dublin, in 1880, a man was discharged after a sojourn in hospital of nine months and nine days. This unfortunate sufferer had as many as forty-two large abscesses on his body as a sequel to an attack of confluent smallpox, but at length he happily recovered under antiseptic and disinfectant treatment. These abscesses are found in all parts of the body, but especially on the extremities, about the buttocks and loins, about the shoulders, and on the scalp. Occasionally an ischiorectal abscess forms, eventuating in fistula. The accompanying pain and discomfort may not be great, particularly if the warm-bath treatment to be afterwards described is carried out. Nor is the constitutional disturbance necessarily excessive, although Trousseau[27] speaks of sudden rigors and increased pyrexia ushering in this complication.

Erysipelas is a serious, and used to be a somewhat frequent complication of the scabbing and desquamation stages. It attacks the face and scalp, occasionally the scrotum. The accompanying pyrexia is apt to run high and may quickly shatter the remaining strength of the patient, who sinks from exhaustion. Another dangerous element is the depth to which the erysipelatous inflammation is wont to penetrate, constituting phlegmonoid erysipelas and perhaps giving rise to diffuse cellulitis. It is easy to see how fertile a soil the Streptococcus

erysipelatos of Fehleisen finds in the seared and scarred skin of a smallpox patient, whose powers of resistance are reduced to the lowest ebb.

Boils are one of the plagues of the later stages of variola. Trousseau referred their appearance to the presence of a true "furuncular diathesis," and this special complication or sequel is now known as "acute furunculosis." It has been already stated that this troublesome morbid state is due to a secondary infection by the ordinary pus cocci, and especially by Staphylococcus pyogenes aureus (Sternberg).

Bedsores have become infrequent in smallpox since skilled nursing has been introduced, and attention has been paid to the necessity of strict cleanliness and to the hygiene of the sick-room. A "bedsore" may be regarded as a local gangrene of the skin and soft parts, due to malnutrition, impaired innervation, pressure, want of cleanliness, and, above all, to an invasion of saprophytic bacteria assuming under such conditions a pathogenic energy. Gangrene is a very rare complication of smallpox. If it occurs, the scrotum is nearly always the part affected.

Brownish discolorations of the skin—pigmentation from acute dermatitis—often persist for a long time after smallpox, and a troublesome and obstinate *acne pustulosa* may develop on the face, particularly over the bridge and along the sides of the nose.

Trousseau attaches considerable prognostic importance to the extreme *swelling of the hands and feet* which commonly follows salivation and swelling of the face in confluent smallpox. According to that great physician, if this swelling fails to appear, the patient dies, if not always, at least nearly always. In this opinion he agrees with Sydenham, Morton, van Swieten, and Borsieri. This swelling of the extremities sets in at the close of the ninth day with severe pain, which becomes very violent on the eleventh or twelfth day and lasts until the thirteenth or fourteenth day, when swelling and pain subside together. Like the swelling of the face, this œdema of the hands and feet depends on the maturation of the pustules. The pain is caused by the extreme tension which results from the formation of pustules under the dense fascia of the palms of the hands and the soles of the feet.

The Eyes.—The eyelids may become the seat of abscesses, or they may slough as the result of pressure from swelling or œdema, caused, it may be, by the presence upon their external surface of even two or three pustules. The organs of vision themselves may be affected in various ways. In the first place, catarrhal or simple acute *conjunctivitis* may occur during or after an attack of smallpox. Its direct cause is in many cases an irritation by retained unhealthy secretions

owing to œdema of the eyelids. In other instances it results from pustulation. Ernst Fuchs states that smallpox pustules not infrequently develop upon the conjunctiva, generally upon the tarsal conjunctiva near the intermarginal line. Smallpox pustules which form upon the conjunctiva of the eyeball, near the limbus, are dangerous because they are likely to set up a purulent keratitis in the adjacent part of the cornea—a condition which, however, should not be confounded with the corneal abscesses that develop metastatically in variola.

The late Professor Horner, of Zurich, studied the subject of the conjunctival complication of smallpox during the epidemic of 1871. His views are quoted by Mr. H. R. Swanzy, of Dublin, in his "Handbook of the Diseases of the Eyes and their Treatment." Mr. Swanzy reminds us that a good deal of uncertainty prevailed previously, for the initial stages of the eye affection were not carefully observed by physicians, owing to the swelling of the eyelids, while the ophthalmologist saw only the results of the process in the period of convalescence.

Smallpox pustules on the cornea are, Horner believes, extremely rare; indeed, he has seen but one case. According to him, the most frequent and most serious mode of attack consists in a grayish-yellow infiltration in the conjunctiva close to the lower margin of the cornea, not extending to the fornix conjunctivæ or far along the inner or outer margin of the cornea. This infiltration occurs in the eruptive stage and is to be regarded clinically as a variola pustule. It gives rise to a corneal affection, as does a solitary marginal phlyctenula, either in the form of a marginal ulcer or as a deep purulent infiltration, ulcerating, perforating, leading to staphyloma, purulent iridochoroiditis and panophthalmitis—results which are often observed for the first time long after the primary conjunctival affection has disappeared. Horner considers that the morbific germ of the conjunctival infiltration makes its way between the eyelids, and that the constancy of the position of the infiltration, below the cornea, is accounted for by the fact that that part of the conjunctiva, when the eyelids are closed and the eyeball is consequently rotated upwards, is the most exposed to the entrance of foreign particles. Lastly, Horner believes that the frequency with which the eyes become affected varies in different epidemics.

Hebra is of opinion that, although the structure of the conjunctiva is, of course, analogous to that of the other mucous membranes, it is only in very exceptional cases that we find it affected by smallpox. At most a very few pustules may be found on the margins of the lids, close to the roots of the eyelashes and the structures of the

Meibomian glands. The membrane covering the eye may now and then display a pustule the size of a pin's head, very superficial and filled with a yellow fluid. This, however, quickly bursts, being macerated by the conjunctival moisture, and is not followed either by an excoriation of any size or by any disease of the subjacent structures. Hebra's experience on this point must be unique, for he says that he can positively assert and prove from the records of more than five thousand cases of smallpox that even the superficial pustular affection just described occurred in only *one* per cent. of the cases in question, and never caused any even transient injury to, or disfigurement of, the eye itself. He holds that when eyesight is lost in smallpox, this is the result, not of an ulcerative action extending from the conjunctival surface to the deeper parts, but of the formation of metastatic deposits within the eye occurring as a sequela of the disease.

Inflammation of the cornea, or *keratitis*, is usually met with in the later stages of the disease or as a true postvariolous affection. Rarely, it is caused by pustulation; more commonly it results from atrophy from impaired nutrition, leading to ulceration. To this form of the lesion the term "atrophic keratitis" is applied. Perhaps the most frequent cause is metastasis, which is thus described by Ernst Fuchs: "Infection by way of metastasis—*i.e.*, by germs which are circulating in the blood (endogenous infection)—forms the basis of those abscesses which occur in acute infectious diseases, such as smallpox, scarlet fever, measles, typhus, etc. The form of abscess that results from variola is most frequently observed. In this case it makes its appearance, not at the height of the disease, but in the stage of desiccation, and in fact sometimes even in patients who have already left their beds. Hence it follows that it is not to be regarded as a smallpox pustule that is localized upon the cornea. Metastatic abscesses are found in children as well as in adults, and not infrequently affect both eyes so that total blindness can be produced by them."

As true postvariolous eye affections, Horner recognizes diffuse keratitis, iritis and iridocyclitis, with opacities in the vitreous humor, and glaucoma. The globe may suppurate (panophthalmitis), causing loss of sight. In the hemorrhagic form of the disease, hemorrhages may take place into the conjunctiva, constituting sanguineous chemosis, or into and behind the retina, detaching it and so leading to blindness. Lastly, when pyæmia comes on, septic infection of the choroid and of the retina may take place.

The Ears.—The sense of hearing is often impaired in one ear or in both ears. W. Stokes and others have assigned paresis of the auditory nerve and an acute degenerative softening of the intrinsic

muscles of the ear as probable causes of the bilateral deafness so often observed in the course of typhus fever. But these factors do not play so important a part in the production of deafness in smallpox as does the occurrence of an acute or chronic suppurative otitis. This complication may affect one or both ears. Again, caries of the ossicles of the ear—the outcome of an antecedent otitis media—may produce partial or complete loss of hearing. A third and still more dangerous complication or sequela is suppurative thrombosis of the cerebral sinuses, arising, it may be, from extension of disease from the middle ear through the mastoid cells to the dura mater, the cerebral sinuses, and the brain itself.

Septic phlebitis of the sinuses may in turn lead to pulmonary embolism and purulent infiltration of the lung, or, locally, to the formation of a cerebral abscess.

A remote effect of ear trouble is the development of purulent choroiditis and panophthalmitis. These grave lesions are brought about through plugging of the ciliary arteries by minute pyæmic emboli which have been carried from the infarcted lungs through the pulmonary veins into the left ventricle, and thence through the branches of the ophthalmic artery to their final destination.

Respiratory Organs.—The *nose* is sometimes the seat of variolous ulceration in confluent attacks. Epistaxis of course is one of the manifestations of hemorrhage in purpuric or hemorrhagic cases.

Laryngitis—catarrhal, ulcerative, or diphtheritic. The first is generally caused by the presence of an intralaryngeal rash. It comes on during the development of the eruption towards the close of the first week, is ushered in by hoarseness or huskiness, a harsh, dry, spasmodic cough, and more or less tightness of breathing, which in severe cases amounts to urgent and dangerous dyspnœa. Aphonia is an ominous symptom in this complication.

Less frequently, the inflammation of the larynx is diphtheritic in nature; or it may be ulcerative, when it is accompanied by destruction of tissue and may be followed by extension of ulcerative processes to the neighboring tissues. The cartilages are in such instances eroded, when the condition is known as *Perichondritis laryngea variolosa*. At the Pathological Society of London, on April 20th, 1880, Mr. Eve showed a specimen of laryngeal perichondritis which had supervened in the convalescent stage of smallpox in a man aged thirty-six years. Tracheotomy was performed, but the patient died. The epiglottis and arytenoepiglottidean folds were œdematous, and the arytenoid cartilages were necrosed and surounded by pus. In cases in which a vesicular rash develops in and near the larynx œdema of the glottis may occur. This deadly complication is

ushered in by aphonia and is likely to prove fatal, death taking place about the eighth day.

Tracheobronchitis is nearly always present in greater or less degree. It results, as in other fevers, from the general toxæmia; but a much more potent and peculiar cause is the presence of the variolous vesicles, it may be in vast numbers, throughout the whole system of bronchial tubes. When the catarrh extends into the terminal tubes, a dangerous capillary bronchitis or bronchiolitis lights up. In young unvaccinated subjects this may kill by inducing asphyxia in a purely mechanical way. The mucous membranes swell, and the œdema becomes so extreme as effectually to prevent the entrance of air into the pulmonary alveoli. In adults, death may result from continued pyrexia and exhaustion, or from extension of inflammation into the lungs themselves, a widespread *lobular pneumonia* supervening. In the aged, palsy of the bronchi may lead to death by *drowning*, as it were—the secretions not being discharged by cough; or heart embarrassment may result from the mechanical obstruction to the lesser or pulmonary circulation. Under such circumstances hypostatic congestion or consolidation of the lungs may supervene.

Lastly, *pleuritis*, with purulent effusion from the outset, may arise from extension of inflammation from the lungs to the pleura, or from a secondary infection by some of the pyogenic microorganisms. As the serous membranes escape the variolous eruption, we cannot attribute pleuritis to such a cause.

Circulatory Organs.—Among the secondary affections of the circulatory organs we find *pericarditis*, which is, however, very rare in smallpox. *Endocarditis* is a still rarer complication. If it does occur, it is probably due to a secondary infection, the lesion being that described as malignant or ulcerative endocarditis, due to a mycotic invasion of the affected tissues by Staphylococcus aureus or Streptococcus pyogenes. Curschmann has seen ulcerative endocarditis in one confluent case.

Myocarditis occurs, according to MacCombie, in a large number of the confluent cases. It is open to question, nevertheless, whether the change which takes place in the heart muscle in such cases is really inflammatory in nature. It is rather a granular degeneration of the muscle fibres to which the name "cloudy swelling" is now commonly applied. Under the names of "acute parenchymatous degeneration," "albuminous degeneration," "febrile softening of the heart," "infectious myocarditis," Dr. J. Mitchell Bruce,[38] of Charing Cross Hospital, London, some years ago described the acute change in the muscular tissue of the heart which is apt to occur in certain febrile and infective diseases. The opinions of pathologists as to the

nature of this disease have long been, and are still, conflicting, some maintaining that it is truly inflammatory, others that it is degenerative only.

"Parenchymatous myocarditis" is the result of acute febrile and infective processes, such as scarlatina, diphtheria, variola, typhus, typhoid, and relapsing fevers, septicæmia and pyæmia, more rarely measles. The condition may be set up during the later, as well as in the earlier, stages of these diseases, or even during convalescence. In it the heart is sometimes distinctly dilated; the myocardium is of a dirty grayish-red or grayish-yellow color, with occasional extravasations; its consistence is soft; its substance is lax, flabby, and friable. Thrombi may be found in the ventricles. Microscopically, the muscular fibres are swollen, their striation is more or less lost and replaced by granular (albuminous) and fatty molecules; occasionally they undergo waxy degeneration (Zenker). Along with these evidences of degeneration there are found certain appearances which suggest regeneration. Lastly, the blood-vessels are dilated and are the seat of thrombosis, with obliterative endarteritis of the arterioles.

Dr. Bruce points out that the pathological connection between this acute parenchymatous change and its cause is still unsettled. It may be the result of the specific action of the several poisons, or of the pyrexia, or of both, on the protoplasm. It is closely related to fatty degeneration of the heart—indeed, if the destructive part of the process be in excess, the change rapidly proceeds to fatty degeneration, which then covers, or takes the place of, the other changes.

As regards the symptoms, cardiac failure is the chief evidence of this condition of the myocardium.

Hemorrhages—(α) cutaneous; (β) from mucous membranes; (γ) from serous membranes. It has been shown above that the purpuric manifestations and bleedings of malignant smallpox have been variously explained. Older observers held that the blood is in these cases destroyed by the variolous poison—a condition of acute hæmatolysis being induced. The modern school, represented by Klebs and Unna, maintain that the phenomena in question result from a bacterial coagulation thrombosis (see page 425).

In the series of drawings of smallpox by Mr. J. Conolly, of Dublin, to which allusion has more than once been made in this article, hemorrhages into the skin, the mucous membranes, and the serous membranes have all been portrayed with artistic fidelity and skill.

Venous thrombosis is an occasional sequel, causing phlegmasia alba dolens, or "white leg." This condition may also, however, depend on obstruction of the lymph channels or inflammation of the subcutaneous areolar tissue (diffuse cellulitis).

Digestive Organs.—Secondary affections of the digestive organs are uncommon in smallpox.

The *tongue* may be enormously swollen, so as to protrude from the mouth and seriously to impede both respiration and deglutition. In extreme cases the dysphagia may be complete, rendering it necessary to support the patient by rectal feeding. The œdema of the tongue is symptomatic of a true *glossitis*, due to the presence of a variolous rash in the mouth and affecting the tongue itself. It is a painful affection, and not less dangerous than painful. Ulcerative stomatitis commonly accompanies the glossitis in these cases. The salivary glands are occasionally inflamed, but this is not a serious complication.

When the intestines are the seat of a thick-set variolous eruption, *diarrhœa* is very likely to occur. It is a dangerous complication, likely to cause death, particularly in young unvaccinated children. *Colitis* may be attended by dysenteric discharges—offensive, mucoid, and sanguineous. Sydenham speaks of a *variola dysenterica*.

Hæmatemesis or *melæna* may accompany hemorrhagic or purpuric smallpox.

Peritonitis has been occasionally observed. MacCombie saw extensive peritonitis in two cases after abortion, also in an adult male along with pleurisy. In a fourth case he found peritonitis limited to the left hypochondrium and epigastrium in a patient whose spleen was studded by large emboli.

Kidneys.—The secondary affections of the renal organs which call for remark are: *Albuminuria*, which is not infrequent in the acute stages of the severer forms of the disease. This symptom does not necessarily imply the presence of kidney disease, for with the excessive blood changes which may occur in bad smallpox no less than in bad typhus, blood serum may find its way into the urine. According to Abeille (quoted by Trousseau) albuminuria is present in about one-third of the cases.

Hæmaturia is a common symptom in purpuric smallpox.

Acute nephritis is a rare complication or rather sequela, for it is more likely to occur in convalescence than in the acute stages of the disease.

Cystitis has been observed, especially in cases in which there has been retention of urine, either from inattention in delirious cases or from paralysis of the walls of the bladder. The latter accident is not at all so usual in smallpox as it is in typhus fever.

Nervous System.—Among secondary affections of the nervous system, *delirium* occupies the first place. It is usually unassociated with meningitis and depends on the direct influence of the variolous poison

on the brain, or on the disordered and impaired blood supply of the nervous tissue, or on pain and sleeplessness, particularly in the pustular and crusting stages of confluent smallpox. As has been already stated, the raving in this disease is often violent and noisy (*delirium ferox*), less frequently busy with muscular agitation (*delirium tremens*); in the later stages, of the low muttering type (*typhomania*). Trousseau said he did not fear delirium if the pulse maintained its volume and did not become rapid, and if sweating continued; but if the skin is dry and cold—if the pulse loses its proper strength and becomes small, sharp, or irregular, the delirium has a very different meaning, and is a certain sign of approaching death.

Meningitis is rarely met with. Its existence may be inferred from the following symptoms: excruciating headache, delirium, morbid acuteness of the senses, signalized by extreme intolerance of light (photophobia) and of sound, bounding pulse, nausea and vomiting, loud cries and screams (*cri cérébral*), as well as strabismus, ptosis, opisthotonos, and partial palsy. A red streak is often left upon the skin after pressure by the finger. This symptom is known as the *tache cérébrale*, or cerebral stain.

Trousseau mentions the case of a woman, who, during the progress of modified smallpox, presented no disturbance of the nervous system, except attacks of *acute mania* without fever. In 1878 Seppilli and E. Maragliano[39] reported three cases in which insanity followed an attack of smallpox. One patient remained incurably insane. The others recovered after a course of appropriate treatment. In a fourth case, on the other hand, the patient was a violent maniac and under treatment in a lunatic asylum from April 12th to June 1st, 1877. At the latter date he was seized with smallpox of the confluent type. The disease went through its usual stages, but during its progress the maniacal symptoms subsided and were succeeded by the most complete tranquillity. The eruption disappeared in due course, and on the passing off of the attack of smallpox the patient was restored to the full possession of his mental faculties and was discharged from the asylum a sane man.

According to Trousseau, in a great many cases the lumbar pain (rachialgia) of the initial stage is accompanied by *paraplegia*. The patients themselves mention this paralysis without suggestion by the physician. They complain of painful numbness in, and inability to move, the lower extremities. The motor power is in no way impaired in the upper extremities. The bladder is sometimes involved, as is shown by retention of urine, or at least by great dysuria. The paraplegic symptoms are generally of short duration, ceasing spontaneously when the rash appears. In some

cases they last till the ninth or tenth day; in others they persist throughout the whole attack, constituting, it may be, a sequela as well as a complication.

Peripheral neuritis is very rare in smallpox. To such a lesion, however, Combemale[40] would attribute certain of the disorders of speech which are occasionally observed in variola. This author has been able to collect only ten examples of variolous speech disorders. In a girl, aged twenty years, the temperature was very high throughout an attack of smallpox, and the delirium was marked. On the twelfth day a certain slowness in articulation was noticed; the voice was somewhat nasal in character, and there was a slight but apparently fleeting internal strabismus. The uvula deviated to the left and was insensitive. There was much difficulty in framing answers to questions. On the twenty-fifth day the difficulty in speech still persisted, and the left upper eyelid drooped a little. The labials and dentals were badly pronounced. In two months' time the improvement was very considerable. The author refers to two cases reported by Saint-Philippe, in which the difficulty in speech occurred quite early in the disease, namely, during the invasion. In both cases there was also difficulty in swallowing, and in one case a paraplegia from which the patient recovered in a month's time. In two cases, both in women a little over forty, reported to the Clinical Society of London in 1886 by Whipham and A. T. Myers,[41] the difficulty in speech appeared during the eruption, and there was in addition some loss of power in the extremities. When speaking, the syllables were scanned or "squeezed out." These patients recovered only incompletely from the speech affection after a period of six and four years respectively. Combemale thinks that the first three cases were of the nature of a paralysis, and that the last two were ataxic in character. The paralytic affection of the speech, he thinks, is common, but the verbal ataxia is rare. The latter is due to a persistent lesion in the nervous centres, such as minute hemorrhages, but the paralysis he would look upon as due to the effects of the toxins upon the peripheral nerves. If it is accepted that membrane on the palate is a necessary condition for a subsequent paralysis of the palate in diphtheria, so it may be taken that the eruption on the palate and other organs concerned in articulation is necessary to the development of speech defects in variola. Combemale has noticed that many patients speak with a nasal twang during convalescence from variola. Hughlings Jackson suggests that a thrombosis occurring in a minute vessel of the medulla oblongata might best explain the cases recorded by Drs. Whipham and Myers.

Westphal[42] has carefully studied cases of paralysis of the lower

extremities and of the bladder in smallpox, and has shown that the symptoms are often due to numerous circumscribed foci of inflammation in the gray and white matter of the spinal cord (*myelitis disseminata*).

Disseminated Spinal Sclerosis.—Sottas records in the *Gazette des Hôpitaux*, April 12th, 1892, the case of a youth, aged eighteen years, who contracted variola in June, 1891. The rash was discrete, but the nervous symptoms were so severe as to lead to the supposition that meningitis was present. The patient became semicomatose and generally paralyzed. His speech was slow and dragging rather than scanning. There were slight nystagmus, without tremor of the head, and atrophy of the muscles of the trunk and limbs, with great diminution of muscular power. In fact, at this time the paralytic symptoms were dominant, but they disappeared little by little, and gave place to contracture. The reflexes became exaggerated, and there was incoördination of voluntary movement, with the characteristic tremors. At the end of February, 1892, he presented a typical picture of disseminated sclerosis. The sphincters were normal, and common sensibility, the special senses, and the muscular sense were preserved. There were no trophic troubles of the skin. Intelligence was diminished; he was excitable, impatient, and subject to violent fits of rage without much cause. Sottas looks upon the case as a typical example of disseminated sclerosis of infectious origin.

Whether *epilepsy* ever occurs as a real sequela of smallpox is, in Curschmann's opinion, very doubtful.

Dr. Stephen Mackenzie has recorded in *Brain* a case of *anterior poliomyelitis* which occurred after variola.

Genital Organs.—Secondary affections of the organs of generation occasionally occur.

Phimosis has been known to result from œdema of the prepuce, which is sometimes extreme in confluent cases.

Trousseau mentions *orchitis* and *ovaritis*, its analogue in the female, as sometimes developing concurrently with the appearance of the eruption. M. Béraud, a hospital surgeon, treated this subject in a very complete manner in the *Archives générales de Médecine*, March and May, 1859. Trousseau says that we must not restrict the terms *orchitis* and *ovaritis* to inflammation of the parenchyma of the testicle or ovary, but extend it to inflammation of the tunica vaginalis and of the folds of peritoneum which surround the ovaries. The inflammation of these serous membranes results from the variolous poisoning, but is not due, as Trousseau believed, to the presence on the membranes of a smallpox eruption. Variolous orchitis is detected by the patient complaining of pain when the slightest pressure

is made on the scrotum or when he moves. Forthwith, swelling of the parts is perceived and subsequently fluctuation. The pain is said to be less acute when the inflammation occupies the parenchyma of the organ. The symptoms of ovaritis are not so well marked and are less known.

Joint disease, with painful swellings, effusions of serum or pus, inflammation of cartilages and of bones, may occur during or immediately after smallpox. In 1887 Arthur Neve,[43] of the Mission Hospital, Cashmere, communicated a series of cases of bone disease after smallpox in young children. In his paper Mr. Neve makes the astounding statement that probably over seventy-five per cent. of the population of Cashmere die in childhood from smallpox. The cases he reports are these: disease of both elbow-joints and one wrist-joint in a boy, aged three years, simultaneous excisions, cure; complete necrosis of ulna, resection, cure; necrosis of scapula, resection, cure; acute suppuration of shoulder-joint, incision and drainage, cure. Mr. Neve regards the foregoing as fairly typical examples of a class of cases common wherever vaccination is not practised.

Septicæmia and *pyæmia* are rare complications or sequelæ of smallpox. Pyæmia, with purulent deposits in the joints or multiple abscesses, is a fatal complication in the crusting stage or later. Its occurrence may be inferred from the following symptoms: repeated rigors, unstable spiking temperature ranges, extreme prostration, heart failure, an icteroid tinge of the skin and conjunctivæ, and profuse sweating.

Curschmann considers that more has been said concerning pyæmic symptoms in the periods of suppuration and desiccation than is warranted by facts. He has, notwithstanding, seen two unmistakable cases of this kind, in which abscesses in the liver and lungs were found at the autopsy.

Pathology.

The morbid anatomy of the skin and mucous membranes must first be considered.

"Unlike the papule of measles and of most other exanthemata," writes Hilton Fagge, "the papule of smallpox depends upon a definite change in the superficial and middle cells of the rete mucosum, which from the very commencement of the morbid process are swollen and opaque, and in their midst exudation quickly takes place, so that by the end of two days the horny layer of the epidermis is raised to form a minute conical vesicle." Subsequently, the pustule forms as a result of cell proliferation, and a central depression—the so-called umbilicus—develops, at the bottom of which the opening of a hair

follicle or sweat gland is, according to Curschmann, frequently found. This fact suggested an explanation of the formation of the umbilicus, so characteristic of the smallpox pustule. Either of these structures —the hair follicle or the sweat gland—may form a *retinaculum*, tying down the roof of the vesicle in the middle.

This explanation, however, is not always applicable, "since," says Hilton Fagge, "the pock does not necessarily bear a definite relation to any of the canals which traverse the cuticle. In all probability a similar function is then discharged by one of many other bands which cross the upper part of every vesicle in a direction more or less vertical, dividing it into a number of separate chambers" (or *loculi*). "This *loculated* character of the pock attracted notice long before its nature was understood; it affords the reason why only a small part of the fluid is evacuated when a needle is introduced into the roof at a single spot. . . . Auspitz and Basch showed several years ago that all the septa in question are in reality formed out of the original cells of the rete mucosum, small bundles of which adhere together, and become stretched out into filaments and bands, as the exudation accumulates around them. In this fluid leucocytes are present in small number from the very first; they go on increasing, and it gradually passes from transparent serum into opaque pus; the change is complete in about six or seven days from the first appearance of the papule—that is, in the earliest part of the eruption, by the ninth or tenth day of the disease."

The morbid processes in the skin are by no means confined solely to the epidermis. The papillary layer of the derma is also the seat of a variolous inflammation which may have very important and serious consequences. According to von Bärensprung, a hyperæmia extends down through the whole thickness of the skin. The exudation which fills the vesicle and afterwards the pustule is derived from these vascular (hyperæmic) tissues. Some of the papillæ are, according to Curschmann, flattened by pressure, becoming in consequence permanently atrophied. Others, however, are infiltrated by leucocytes to such an extent as to obliterate their nutrient blood-vessels and so to destroy their structure, converting them into a white or ash-gray substance—the *diphtheritic* pock of the German histologists.[44] To prove this, which is an example of so-called *coagulation necrosis*, Rindfleisch gives a drawing from an injected preparation, in which the affected area had failed to receive any of the coloring matter (Hilton Fagge).

The most recent views on the morbid anatomy of the skin in smallpox are those put forward by Unna in his work on "The Histopathology of the Diseases of the Skin." He shows that the poisoned

epithelium in the upper prickle layer of the rete mucosum softens and becomes œdematous from swelling of the protoplasm within the epithelial cells, while a secondary coagulation of the albuminoid bodies set free from the epithelial protoplasm takes place, constituting a fibrinoid degeneration of the epithelium. In smallpox this advances slowly, much more slowly than in chickenpox, and is quickly followed by suppuration. This arises partly from intense inflammation, partly from a secondary infection of the skin by pyogenic microorganisms.

Owing to the slow advance of the colliquation or softening of the prickle cells, other epithelial cells are compressed into trabeculæ or septa, perpendicular in the centre and directed somewhat outwards at the side. The younger epithelial cells of the lower prickle layer meanwhile assume the form of hollow spheres or balloons. Unna accordingly describes the fibrinoid degeneration of the epithelium in smallpox as presenting two forms—*reticulating colliquation* (or softening) and *ballooning colliquation*. The first predominates at the periphery of the pock, the second at its centre.

Umbilication is to be ascribed, in the vesicular stage, in part to reticulating degeneration, in part to epithelial œdema. Of these, the former is often especially developed at the periphery of the pock; the latter is always limited to the periphery. The less swollen centre, where ballooning colliquation predominates, simply remains behind. Unna admits that, where a hair follicle accidentally runs through the centre of the pock, a form of depression may be produced, for the swelling of the prickle layer will here be limited by the cornified neck of the hair follicle. But this exceptional case does not explain the characteristic central depression of the smallpox vesicle, to which the term "umbilication" is applied. This depends on the two changes in the periphery of the pock which have been mentioned—reticular colliquation and œdematous swelling of the epithelium, while ballooning degeneration or colliquation leads only to a very slight increase in the centre of the vesicle. Hence the periphery is prominent, the centre is depressed and apparently retracted. From the fifth day onward the blood-vessels throughout the cutis are dilated. A full stream of leucocytes causes an ever-increasing infarction or plugging of the vesicle or pustule, which is thus converted into an almost solid tissue, or, if the horny layer of the cutis yields, a more or less profuse suppuration lasts for a time or speedily ends in the formation of a crust or scab.

When the scab is thrown off, a persistent trough-like depression is displayed (Unna). The depth of the scar depends on the degree and the duration of the flattening of the base of the pock beneath the pustule and the scab. Hence Unna says that "the rational treatment

to avoid scars should be mainly directed to the aborting of the pustular stage, and the rapid removal of the scab by profuse epithelial new growth."

The liver, kidneys, spleen, and heart muscle undergo important morbid changes. The spleen swells, its pulp becomes soft and of a light red color, in those who die early in the disease. It subsequently resumes its normal appearance except in purpuric smallpox, when it may be found small, hard, of a dirty dark red color, sometimes with white or yellowish follicles (Ponfick[45]). The liver and kidneys are the seat sometimes of cloudy swelling (granular degeneration), sometimes of acute fatty degeneration resembling that produced by poisoning with phosphorus. Fatty degeneration is the more advanced condition in which granular swelling may terminate. These organs may be found normal when death occurs either too soon to permit of degenerative changes, or so late that they have returned to their normal condition. The bile is generally pale and thin in confluent smallpox.

Semmola and Gioffredi, of Naples (Vol. IX., p. 426 of this series) recall the fact that Siderey has recently made a very exhaustive study of the anatomical changes of the liver occurring in smallpox. There is first, he says, an intense congestion of the liver with migration of leucocytes and swelling of the endothelium of the capillaries, and later the hepatic cells participate in the infectious process, presenting lesions varying from simple swelling to complete fatty degeneration. Laure, who has studied the changes in the liver in various infections, found in all cases that the hepatic cells became cloudy and infiltrated with fat granules, the capillaries of the lobule were dilated, and the perilobular connective tissue was hyperplastic. It thus encroached upon the lobule so as to interfere with the circulation and consequently the nutrition of the hepatic cells.

The heart muscle may undergo degenerative changes like those observed in the liver and kidneys. These have been already described above (page 435).

In hemorrhagic smallpox, large or small hemorrhages may be found in nearly all the viscera, ecchymoses in the serous membranes, and extravasations of blood in almost all the mucous membranes.

In the skin, the dark purple spots called vibices and the smaller petechiæ, persist after death, because they result from hemorrhage into and, it may be, under the skin—such hemorrhage being probably caused (as has been shown above) by diapedesis of the red blood corpuscles in the train of bacterial thrombosis.

Diagnosis.

The recognition of smallpox may seem to be an easy matter, and so no doubt it is in a large number of the cases. Every now and then, however, instances occur in which an accurate diagnosis is, at all events for a time, a matter of extreme difficulty. The characteristic symptoms of the disease are masked, or the onset of the attack may present symptoms which are supposed to belong to some other malady, such as measles or scarlatina or typhus among others.

In all cases account should be taken of any prevailing epidemic. We should also inquire whether the patient has been exposed to any special infection and whether he has already suffered from any of the eruptive or continued fevers, the onset or course of which might be mistaken for smallpox, or, conversely, smallpox for them. In this connection it is to be remembered that, as a rule, the various infective diseases, particularly those which are attended by marked pyrexia, confer upon an individual a more or less complete immunity against future attacks. The bearing of this clinical and pathological fact on the question of diagnosis is obvious.

It is in the invasion and early eruptive stages that difficulties usually arise. Having considered the facts relating to the prevalence of any special epidemic at the time and to exposure to any particular infection, the physician will carefully observe the symptoms which are present. A sudden onset, with chills or rigors, headache, severe lumbar or sacral pain, pain in the pit of the stomach, nausea, often vomiting, delirium, constipation, thirst, sweating, furred tongue and fetid breath, with the appearance upon the skin of an accidental erythematous rash, constitute a group of symptoms the presence of which should suggest smallpox.

The morbid states which may be confounded with smallpox, or *vice versâ*, are as follows:

Lumbago.—Rheumatism of the lumbar muscles, especially the erector spinæ, and of the lumbar fascia may be simulated by the backache of smallpox. But lumbago is unaccompanied by fever, headache, or the other initial symptoms of smallpox.

Simple Fever.—The prodromal fever of smallpox may be mistaken for ephemeral or simple fever, which, however, has no rash and generally quickly passes off.

Scarlet Fever.—The onset of both scarlatina and smallpox is sudden and accompanied by headache, nausea, or vomiting, and (in children) diarrhœa. The difficulty of diagnosis is increased when a scarlatiniform rash overspreads the surface. The marked sore throat

of scarlatina is, however, wanting in smallpox, while backache is absent in scarlatina. The enlargement of the papillæ of the tongue so characteristic of scarlatina—constituting the cat's tongue or strawberry tongue of that disease—is not observed in smallpox, in which the tongue is thickly coated with a thick, foul, creamy, or blankety fur. The temperature falls more quickly in smallpox than in scarlatina, when the true rash of the former disease appears.

Measles.—The initial macular rash, and the papular stage of the true rash, may be taken for measles, the marked coryzal symptoms of which are absent; in measles too the fever *increases* as the rash comes out, while in smallpox it *decreases*. At the onset of a papular eruption it is often difficult to decide whether the case is one of measles or smallpox. The following method, called the "Grisolle sign," is a certain means of diagnosis. If upon stretching an affected portion of the skin the papule becomes impalpable to the touch, the eruption is caused by measles; if, on the contrary, the papule is still felt when the skin is drawn out, the eruption is the result of smallpox. The papules of smallpox are hard and shotty to the touch; those of measles are soft and velvety.

The pain in the back is wanting in measles, which usually attacks young children, whereas smallpox commonly occurs among adults. At the beginning, also, confluent smallpox presents its true eruption on the second day, whereas the measles rash does not develop until the fourth or fifth day. H. Koplik,[46] of New York, has recently drawn attention to a characteristic sign of measles occurring on the buccal mucous membrane, which may aid in making a differential diagnosis. During the first twenty-four or forty-eight hours of the invasion of measles a distinct eruption of small, irregular spots of a bright red color is to be invariably seen on the buccal mucous membrane and the inside of the lips. In the centre of each spot, in strong daylight, a minute bluish-white speck is noticed. These specks of bluish-white, surrounded by a red zone, are seen only on the buccal mucous membrane and the inside of the lips, not on the soft or hard palate, the appearances in connection with which are in no way characteristic or pathognomonic.

Typhus Fever.—The onset of smallpox and that of typhus often closely resemble each other. The fever continues and even increases after the appearance of the rash in typhus. The rash in the latter disease also is macular rather than papular. At its first appearance alone is it raised about the level of the skin and then only to a trifling extent. The subsequent course of the two fevers is essentially different. It should not be forgotten also that the eruption in smallpox affects the face in particular, because of its vascularity and exposure,

whereas in typhus the rash spares the face, or is not noticed there, perhaps from the presence of a malar blush, or sunburn, or freckles.

Syphilis.—Strange as it may appear, a macular syphilide—syphilitic roseola—and later on a pustular syphilide have been confounded with smallpox, or the reverse. The clinical history should solve the difficulty without much trouble. The severe initial symptoms of smallpox will be wanting in a case of syphilis, while there will be enlargement of the inguinal glands.

Medicinal Rashes.—In connection with the subject of venereal affections, I may mention that in recent epidemics of smallpox in Dublin, male patients were every now and then sent into Cork Street Fever Hospital as suffering from smallpox, but on examination it turned out that the suspicious rashes, the development and appearance of which caused them to be sent to hospital, were due to the fact that they had been taking cubebs, copaiba, or perhaps iodide of potassium —the rashes were medicinal rashes. The curious pustular eruption which sometimes accompanies the ingestion of iodide of potassium is figured in Plate XXXIII. of the "Atlas of Skin Diseases," published by the New Sydenham Society, London.

Ptomain Poisoning.—Cases of poisoning by meat, milk products, fish, or shell-fish, sometimes present symptoms which in the suddenness of their appearance, their nature, and intensity more or less resemble the onset of variola. Accidental erythemata may also accompany such cases and increase the difficulty of diagnosis. An absence of a history of exposure to infection and a positive history of some error in diet may help to a right conclusion without much delay.

Varicella or Chickenpox.—It is of the first importance correctly to diagnosticate varicella from variola. In cases of doubt, it will be better for the physician to act as if the disease were really varioloid, in order to protect the community.

At this time of day, it seems hardly necessary to insist that varicella is a disease of its own kind (*sui generis*), absolutely distinct from smallpox in all respects. But the glamour which attaches to the name of the great dermatologist of Vienna, Hebra, and to that of his son-in-law, Kaposi—both of whom refuse to recognize the separate identity of chickenpox—renders imperative a statement of the grounds upon which a differential diagnosis is based. Of these the principal are here given after Trousseau's account, contained in his masterly "Clinique Médicale de l'Hôtel Dieu."

1. Chickenpox has often prevailed epidemically without smallpox. Möhl, for example, states that from 1809 to 1823 chickenpox was annually observed at Copenhagen, from which smallpox was absent. On

the other hand, varioloid has never been prevalent without coincident smallpox.

2. As to age, very young children are attacked by chickenpox, whereas smallpox in a population protected by vaccination usually shows itself in adults. If unvaccinated children are attacked by smallpox, it is apt to prove virulent—hemorrhagic or confluent, and to kill speedily.

3. Chickenpox had been described and known long before the introduction of vaccination, previously to which date varioloid was rarely met with.

4. Vaccinated children readily take chickenpox, not so smallpox, even in the form of varioloid.

5. Children who have had chickenpox may contract smallpox even soon afterwards. In the *Lancet* for 1877 a case is recorded of an unvaccinated child, who was admitted into St. Thomas's Hospital for chickenpox, but who was placed on the floor containing the smallpox wards because the diagnosis was at first uncertain. Two days afterwards vaccination was performed, which succeeded. Eight days later still the child fell ill with modified smallpox (Hilton Fagge).

6. The two diseases may coexist. In 1845 Dr. Delpech published a case of this kind.

7. The virus of chickenpox never gives rise to smallpox, and the converse of this proposition is believed to be equally true.

8. Chickenpox is generally held to be non-inoculable, whereas smallpox is notoriously inoculable.

9. Second attacks of chickenpox are not uncommon, while smallpox rarely occurs twice in the same person.

(The opinion of Trousseau here expressed is by no means universally held. For example, Hilton Fagge states that "second attacks of chickenpox are almost unknown." Dr. MacCombie has not seen a second attack, nor has Thomas, of Leipsic, author of the article on "Varicella" in von Ziemssen's "Cyclopædia of the Practice of Medicine." In a long experience I cannot myself recall a single instance in which chickenpox has recurred in a given individual. On the other hand, Gerhardt treated a child for even three attacks of varicella. Heim reports a similar case. Vetter, Kassowitz, Boeck, Hufeland, Canstatt, and Trousseau all report recurrent attacks in the same patient.)

10. The eruption of chickenpox may set in after twenty-four hours, that of varioloid is postponed to the fourth or fifth day.

11. The febrile movement in chickenpox continues after the spots appear, that in varioloid subsides.

12. In chickenpox the spots come out in successive crops and the fever is slight and remittent.

(Plate XLVII. in Willan and Bateman's "Delineations of Cutaneous Diseases," published in London in 1817, affords an excellent illustration of the rash of chickenpox presenting its various stages of development at the same time. In the descriptive letter-press Dr. Bateman writes: "The intermixture of rising vesicles with those that are puckered and subsiding and others that are drying into scabs, on the fifth or sixth day, as here represented, constitutes a principal point in the diagnosis between this eruption and smallpox.")

13. The characters of the spots are essentially different in the two diseases.

14. Chickenpox is not a deadly disease, whereas even the mildest form of smallpox may prove fatal.

The interested reader will find an excellent statement by Dr. Samuel Jones Gee of the arguments in favor of the non-identity of varicella and variola in Vol. I. of Reynolds' "System of Medicine."

Herpes.—That a mistake in diagnosis sometimes occurs between variola and "shingles" appears to me to be tolerably clear from a careful study of a plate in the first volume of Edgar M. Crookshank's "History and Pathology of Vaccination,"[47] reproduced from Dr. Alexander Monro's "Observations on the Different Kinds of Smallpox," published at Edinburgh in 1818, and purporting to represent "smallpox after perfect vaccination." So far as the illustration is concerned, it is impossible to suppose that the "rash" portrayed on the face is anything else than crops of herpetic vesicles. Their distribution on the right side of the face only, and along the supraorbital branch of the fifth nerve and the facial nerve, together with their appearance, size, and grouping—all go to support the view that the affection is herpes zoster. It is not denied that the patient, who was Dr. Monro's eldest son, aged fifteen years, had smallpox. This is evident from the clinical report of the case with the concurrent testimony of Dr. Rutherford and Mr. Bryce, the latter justly considered one of the greatest authorities of the day on smallpox. Indeed, three of Dr. Monro's children had varioloid at the same time. All that is contended for is that the patient in question suffered from shingles in addition to varioloid.

Erysipelas.—The vast and unsightly swelling of the face in confluent smallpox is very like erysipelas, but a careful physical examination would set the question of diagnosis at rest.

Glanders.—Dr. Robert Liveing says that, of all diseases, perhaps glanders in an early stage is the one most likely to be mistaken for smallpox. The febrile symptoms are like those of smallpox, and the

rash consists of hard infiltrations in the skin and mucous membrane, which quickly suppurate and form deep and inflamed ulcers. When these infiltrations are small and scattered, and before ulceration has begun, the difficulty of a diagnosis is by no means slight. Glanders is a rare disease and usually occurs in grooms and stablemen. The rash comes out in *successive* crops and ulcerates rapidly.

Acne Pustulosa.—Curschmann includes this skin disease among the affections which have to be distinguished from smallpox. The local distribution of the acne papules and pustules on the face, neck, and shoulders; the absence of the initial symptoms of variola, and the comparative chronicity of acne serve as grounds for a diagnosis.

Pemphigus wants the symptoms of smallpox. The bullæ or blebs are generally larger than variolous pustules. The onset and course of the two diseases are entirely different. The blebs appear in successive crops, often sparing the face, hands, and feet. The acute form of the disease is almost peculiar to children.

Acute rheumatism, when accompanied by erythematous or purpuric rashes, or by abundant crops of sudamina or miliary vesicles, may simulate variola by reason of the pains, the pyrexia, and the sweating. In a short time, however, all difficulty will vanish, as the course run by the two diseases is essentially different.

Meningitis, according to Curschmann, may resemble quite closely the initial stage of variola. In both diseases we have intense headache, vertigo, delirium, coma, and convulsions. The most doubtful cases are those of meningitis of the convexity extending over both hemispheres and without localizing symptoms. The rash of smallpox is wanting, and the fever runs on in meningitis. The difficulty of diagnosis is much increased in cases of epidemic cerebrospinal meningitis, in which erythematous and purpuric rashes may appear. The following clinical observation will illustrate this statement:

Francis M'G——, aged 15 years, was admitted to one of the smallpox wards at Cork Street Fever Hospital, Dublin, on Tuesday evening, April 27th, 1880. He was a draper's assistant. His illness began about noon on Saturday, April 24th. While at work he was suddenly attacked by pain in the small of the back, with headache, nausea, and vomiting. In the evening his throat felt very sore. Next day he became worse, having no appetite and complaining of continuous headache, backache, and sore throat. He was removed to the hospital on Monday. On the next day (Tuesday) a rash appeared (fourth day of illness). On the backs of the hands and forearms were numerous nodules and irregular patches of eruption, pink, readily effaced, and distinctly elevated—at least on the hands. Scattered over the legs were numerous punctiform hemorrhagic patches. His face was flushed, but there was no eruption on it. A provisional diagnosis of purpuric smallpox was made, so that the patient was sent

to Cork Street Hospital, where he was placed, as a case of variola, under the care of my colleague, the late R. J. Harvey. On Wednesday morning, April 28th, the fifth day of the attack, Dr. Harvey at his first visit recognized so many anomalies in the symptoms that, believing the case was not one of smallpox, he left a message for me to see the patient. I accordingly did so. The pulse was now 120, the axillary temperature was 104.6° F.; the tongue was thickly furred and the papillæ were red and enlarged, as in scarlatina. The mucous membranes over the fauces, palate, and pharynx were deeply injected, showing here and there patches of whitish exudation. At this time he complained of only slight headache and of very little pain in the back. There was, however, a decided stiffness of the nape of the neck, with retraction of the head; occasional jerking of the muscles of the neck and face was noticed. The bowels were obstinately confined. A profuse eruption covered the body in general, but in particular the back and the posterior aspect of the legs and arms. The eruption was of a deep rose color and consisted of more or less elevated maculæ. The spots varied in size from very small papules (on the neck) to patches as large as a florin and of irregular outline. They showed a tendency to coalesce, were slightly elevated—at least at the edges, which were whitish like the wheals in urticaria—and in many cases had a distinct reddish or even purple centre. They were readily effaced on pressure. The patches of eruption were best seen on the back, the extensor aspect of the forearms, the elbows, and buttocks. On the inner and front part of each shin was a punctiform hemorrhagic patch. The eruption was markedly absent from the face, only one small patch on the lower lip above the chin being observed.

The appearance of the eruption, the marked cerebrospinal symptoms, and the history of the attack at once recalled to mind the cases of epidemic cerebrospinal meningitis which I had seen at the Meath Hospital in 1867, under the care of Drs. Stokes and Alfred Hudson. At all events it was clear that the patient was not suffering from smallpox, and accordingly he was removed without delay to the non-infectious fever ward in the fever hospital. There he passed through several days of dangerous illness, in which all the symptoms of meningitis—including cerebral vomiting and the *tache cérébrale* or line left after drawing the finger sharply across the skin—were present. On May 5th (the twelfth day) he recovered consciousness. The preceding days were to him a blank. The last thing he remembered was his being carried from the smallpox wards to the fever hospital.

The patient continued to go on well until the 9th of May—the twelfth day after his admission to the smallpox wards. On the evening of this day the temperature began to rise, reaching 104.8° F. on the evening of the 11th, when the rash of variola discreta appeared. The disease ran a favorable course, but the pustules were of an unusually large size. On the 15th and 16th of May the temperature rose again, when the throat became very sore. Patches of diphtheritic exudation now appeared on the fauces and uvula, which was considerably elongated. The throat was much better in a few days

and the patient speedily convalesced. He left the hospital quite well on June 18th, 1880, fifty-two days after admission.

That the original malady from which F. M'G. suffered was not smallpox with marked cerebrospinal symptoms is proved by the occurrence of an undoubted attack of smallpox twelve days after exposure to the contagion of that disease. The mode of onset—sudden, with pain in the head and back, nausea, and sore throat; the subsequent development of such nervous or ataxic symptoms as retraction of the head, stiffness of the neck, muscular twitchings, throbbing of the carotids, spasmodic vomiting, and the cerebral stain; and lastly, the peculiarities of the rash—all justify the opinion that the first attack was probably one of exanthematic cerebrospinal meningitis.

Malignant or *ulcerative endocarditis*, when accompanied by an erythematous or purpuric rash, may give rise to a suspicion of smallpox. But symptoms of pyæmia will probably have been already present, and the intensity of the fever and the profound prostration of pyæmia will help the diagnosis.

Prognosis.

In prevaccination times smallpox was infinitely more destructive to life than it has since become. No epidemic disease was so much dreaded in olden times from its loathsomeness as well as from its dangerous nature. Vaccination has acted beneficially in more ways than one. It has protected young children, we may say absolutely, against smallpox; or, failing that, its influence has substituted varioloid for the fatal variola vera in both children and adults.

The mortality from smallpox depends on: (1) The patient's state as regards previous protection by an attack of natural smallpox, by inoculation, or by vaccination; (2) the virulence of the disease itself—the hemorrhagic form being the most deadly, next the purpuric form, then the confluent form; (3) the general hygienic condition or otherwise of the patient's surroundings; (4) the presence or otherwise of complications.

Smallpox is most fatal to unvaccinated children under five years of age and to unvaccinated adults over thirty years. It is estimated that 50 per cent. of the confluent cases, and 100 per cent. of the malignant cases, perish. The influence of vaccination for good is unquestionable—the mortality being 50 per cent. among the unvaccinated in general, 26 per cent. among the badly vaccinated, and only 2.3 per cent. among the efficiently vaccinated.

In Sheffield, in the outbreak of 1887–88, of 4,703 cases, 474 proved fatal, or 10 per cent.; of 4,151 vaccinated patients, 200 died, or 4.8 per cent.; of 552 unvaccinated patients, 274 died, or 49.6 per cent. (Barry[17]).

Hemorrhagic or malignant smallpox may kill in four, five, or six days from the earliest symptoms. In confluent smallpox, on the contrary, the patient seldom dies before the eleventh day, and in general, according to Trousseau, the most fatal epochs are the twelfth, thirteenth, and fourteenth days.

In the case of a disease like smallpox, in which the blood is poisoned and destroyed from the outset, it goes without saying that defective sanitary surroundings—such as overcrowding, want of ventilation, bad house drainage, and so on—must enormously increase the patient's risk.

Again, the complications and sequelæ of the disease often slay the unfortunate individual who had escaped from the perils which beset the earlier part of his passage through smallpox. Œdema of the glottis, perichondritis laryngea (inflammation of the cartilages of the larynx), bronchitis (especially in winter), and diarrhœa may kill straight off; while pyæmia, septicæmia, and the furuncular diathesis may exhaust the patient's strength after weeks or even months of suffering.

In his Medical Report of Cork Street Fever Hospital, Dublin, for the year ending March 31st, 1880, Dr. Reuben J. Harvey included a table showing how protracted was the stay in hospital of many of the non-vaccinated patients who ultimately recovered from smallpox. The high death-rate among the unvaccinated cases, fearful as it is, is not the only calamity the victims of a smallpox epidemic have to encounter. In the year named, fifty out of seventy-four unvaccinated patients died in the hospital. Of the twenty-four who recovered, one-half were detained in hospital for a period of from one to three months; and boils, abscesses, and eye affections occurred in these cases with a frequency and severity altogether out of proportion either to their numbers or to the apparent severity of the primary attack.

In the medical report of the hospital for the following year (ending March 31st, 1881) I gave a similar table, which illustrated the tediousness of the recovery of several non-vaccinated patients, who indeed escaped with their lives, but were fated to pass through weeks or months of suffering before they were fully convalescent. In one case sixty-eight days, in another seventy-seven days, and in a third one hundred and six days were spent in hospital by these victims of non-vaccination smallpox. Even this was surpassed in the case of a man who was discharged after a sojourn of nine months and nine days.

This unfortunate sufferer had as many as forty-two large abscesses on his body as a sequel to the smallpox, but at length he happily recovered under antiseptic treatment.

My medical report of Cork Street Fever Hospital for the hospital year ended March 31st, 1881, contains a series of tables relating to the epidemic of smallpox which was fast waning at the date mentioned. It may prove of interest to quote some of the facts contained in those tables, as they bear directly upon the question of prognosis. Within fifty-three months, from November, 1876, to March, 1881, inclusive, 2,801 smallpox patients were admitted to the epidemic wards. In the year ended March 31st, 1879, the admissions were 1,509, and the deaths 357, or 23.6 per cent. In the next year, 1879–80, the admissions were 600, and the deaths 119, or 19.8 per cent. In 1880–81 the admissions fell to 411, but the deaths were 88, or 21.4 per cent. Table I. and those which follow it illustrate the principal facts connected with the epidemic as observed in the hospital from its commencement to the close of the official year, 1880–81.

In the table the disease is classified as "discrete," "confluent," and "malignant." There were 1,625 discrete, 857 confluent, and 333 malignant cases. Of the large number of discrete cases only 14 proved fatal, the mortality not being *one* per cent. (0.8); whereas of 857 confluent cases 344 ended in death, the mortality being 40.1 per cent.; and of 333 malignant cases 253 died, the mortality rising to 75.9 per cent.

Table I.—Showing the Relation Between the Type of the Disease and the Mortality.

From April 1st, 1876, to March 31st, 1881.

Varieties.	Number of cases.	Proportion per cent. of all the cases.	Recovered.	Died.	Mortality. per cent.
Discrete	1,625	57.7	1,611	14	0.8
Confluent	857	30.5	513	344	40.1
Malignant	333	11.8	80	253	75.9
Total	2,815	100.0	2,204	611	21.7

In Table II. we have statistics as to the relative incidence of the different forms of the disease on the sexes.

The most striking feature in this table is the perceptibly higher rate of mortality among the malignant cases in females than in males. This was no doubt due to the occurrence of abortion, or of premature confinement with hemorrhage, or of menorrhagia.

TABLE II.—SHOWING THE RELATION BETWEEN THE SEX OF THE PATIENTS, THE TYPE OF THE DISEASE, AND THE MORTALITY.

From April 1st, 1876, to March 31st, 1881.

SEX.	DISCRETE.			CONFLUENT.			MALIGNANT.			TOTAL.			
	Total.	Died.	Mortality, per cent.	Total.	Died.	Mortality, per cent.	Total.	Died.	Mortality, per cent.	Total.	Recovered.	Died.	Mortality, per cent.
Males	896	6	0.6	471	194	41.1	178	133	74.7	1,545	1,212	333	21.6
Females	729	8	1.0	386	150	38.9	155	120	77.4	1,270	992	278	21.9
Total.....	1,625	14	.8	857	344	40.1	333	253	75.9	2,815	2,204	611	21.7

The third table brings out two interesting points: first, the lessening severity of the disease as it attacks vaccinated individuals toward the close of the epidemic; secondly, the notably larger proportion of unvaccinated males who suffered from confluent smallpox. Taking the whole epidemic, we see that 24 per cent. of vaccinated males and 23.8 per cent. of vaccinated females had the disease in a confluent form; while in the year ending March 31st, 1881, the corresponding figures were only 10.1 per cent. of vaccinated males and 11.1 per cent. of vaccinated females. The milder type of the disease among unvaccinated cases is also shown to a less extent.

TABLE III.—SHOWING THE RELATION BETWEEN VACCINATION, THE SEX OF THE PATIENTS, AND THE TYPE OF THE DISEASE.

From April 1st, 1880, to March 31st, 1881.

	MALES.			FEMALES.		
	Total.	Confluent.	Per cent.	Total.	Confluent.	Per cent.
Vaccinated.....	168	17	10.1	179	20	11.1
Unvaccinated	33	18	54.5	31	13	41.9
Total.....	201	35	17.4	210	33	15.7

From April 1st, 1876, to March 31st, 1881.

Vaccinated	1,276	307	24.0	1,027	245	23.8
Unvaccinated	269	164	60.9	243	141	57.9
Total.....	1,545	471	30.4	1,270	386	30.3

Again, during the entire epidemic, 60.9 per cent. of unvaccinated males suffered from confluent smallpox, compared with 57.9 per cent. of unvaccinated females. In 1880–81 the difference between the

sexes was even much more striking—namely, 54.5 per cent. of males, and 41.9 per cent. of females.

Table IV.—Showing the Relation between the Ages of the Patients, Vaccination, and Mortality.

From April 1st, 1876, to March 31st, 1881.

Ages.	Total.	Per cent. at each age.	Vaccinated.	Per cent. vaccinated.	Died.	Mortality, per cent.
Under 5	206	7.3	75	36.4	134	65.0
5 and under 10	294	10.4	205	65.9	75	25.5
10 " " 15	379	13.1	336	88.6	33	8.7
15 " " 20	632	22.4	570	90.1	67	10.6
20 " " 30	885	32.1	770	87.0	178	20.1
30 " " 40	268	9.5	226	84.3	80	29.8
40 " " 50	106	3.7	87	82.0	30	28.3
50 and upwards	45	1.5	34	75.5	14	31.1
Total	2,815	100.0	2,303	81.8	611	21.7

In Table IV. the controlling influence of vaccination over the fatality of smallpox is still further exemplified, and in this instance in connection with the question of age. In the year 1880–81, 32 children under five years of age were admitted, of whom only 13—or but 40.6 per cent.—were vaccinated. Twenty of these children died, the death-rate being 62.5 per cent. During the entire epidemic the corresponding statistics are—admissions, 206; cases vaccinated, 75—being only 36.4 per cent.; deaths, 134—mortality being 65 per cent. Can there be any doubt that these enormous death-rates were due to non-vaccination and to tender age? Looking down through the table we find that the lowest death-rates correspond with the periods of adolescence and the prime of life, when also the percentage of vaccinations reaches a maximum of about 90. The high ratio of vaccinated cases in advanced life is shown by the table to notably reduce the fatality, which in old age might be expected to become excessive.

A fair idea of the hospital mortality of smallpox may be gathered from the returns of Cork Street Fever Hospital. Three epidemics of the disease have visited Dublin since 1871. The first began in February, 1871, on the 26th of which month the first case was admitted to Cork Street Hospital. Two years later the outbreak ceased, the last case having been admitted in February, 1873. The total number of cases treated was 740. Of these 563 recovered and 162 died. One patient was removed from the hospital while still suffering from the disease. Assuming that this patient recovered, the death-rate was 21.7 per cent.

The second epidemic began in August, 1876, on the 15th of which month the first case admitted to the hospital came in under my care. Two other cases had previously occurred in Dublin, the first of all being a woman from Manchester, who gave smallpox to a girl who at the time was a patient in the hospital where she was treated. This poor girl died, having meanwhile conveyed the disease to the first case admitted to Cork Street Hospital. The last case admitted came in on April 30th, 1881. The patient was a little girl, *never vaccinated*, who had travelled from London (where smallpox was then prevalent) to Dublin a few days—certainly not more than a week—before she sickened of confluent smallpox. She unfortunately died on the eleventh day. Between the dates mentioned—August, 1876, and April, 1881—the total admissions were 2,816, and the deaths numbered 613. These figures give a death-rate of 21.8 per cent., which is practically identical with that recorded in the first epidemic. The slight discrepancy between the figures in Table IV. and those here given arises from the addition to the former of one admission in April, 1881, and of two deaths in that month—2,815 thus becomes 2,816, and 611 becomes 613.

The third and most recent epidemic began in June, 1894, and ended in February, 1897. Within this period 1,019 cases were admitted and 121 died, giving a death-rate of 11.9 per cent. The marked reduction in the mortality in this last outbreak is no doubt largely due to excellent nursing, to improved hospital accommodation, and lastly to a more general practice of revaccination in the interval between the former epidemic and that under notice.

In a tabular form the facts come out thus:

TABLE V.

Epidemics.	Cases admitted.	Cases died.	Mortality per cent.
1871 to 1873	746	162	21.7
1876 to 1882	2,816	613	21.8
1894 to 1897	1,019	121	11.9
Totals and mean	4,581	896	19.6

Treatment.

This subject naturally falls under the two headings—preventive treatment or prophylaxis, and curative treatment or, preferably, management.

Preventive Treatment.

The principles of the prophylaxis of smallpox are based upon two facts in the natural history of the disease; namely, (1) smallpox is eminently communicable; (2) one attack usually protects an individual from a second attack—in other words, it confers immunity upon him.

Early information of the outbreak of so catching a disease as smallpox is essential if its spread is to be checked. Therefore notification to the sanitary authorities should be made compulsory everywhere, as recommended in the report of the Royal Commission on Vaccination (1896). The prophylaxis of any acute specific fever consists in (1) the destruction of the virus or contagium before it can effect an entrance into the system; (2) the adoption of measures which will have the result of lessening the receptivity of the individual, or his susceptibility to the disease by increasing his powers of resistance; and (3) the strict enforcement of rules relating to quarantine and isolation. "Quarantine (no longer used with its original signification of a forty days' detention) means the segregation of *possibly* infected persons until after the period has elapsed at which they would (if infected) develop characteristic signs of the disease. Isolation, on the contrary, implies the continued separation of the infectious patient from the healthy until after he has ceased to be infectious" (Shelly[48]).

The destruction of the virus or contagium of infectious diseases is achieved by disinfection, using the term in its strict etymological sense to denote any process by which the contagium of a given disease may be destroyed or rendered inert, so as to render impossible the spreading of that disease. The poison of smallpox is very resistant to ordinary means of disinfection, and so far as body clothing is concerned, the safest plan appears to be absolute destruction by fire. In fatal cases the corpses should be wrapped in sheets thoroughly moistened with a standard solution (1:1,000) of perchloride of mercury (corrosive sublimate). Bed linen and other articles which admit of washing should be folded without shaking or making a dust and placed in sheets dipped in the corrosive-sublimate solution. They should then, without unwrapping, be boiled for half an hour in a strong solution of soft (potash) soap. After the sick-room has been vacated, the floor, walls, windows, door, furniture, etc., must be rubbed with cloths, sponges, or brushes dipped in the solution of corrosive sublimate, and afterwards cleansed with the potash soap.

Upholstered furniture, cushions, mattresses, curtains, and other things which cannot be washed, are to be disinfected in specially constructed disinfecting-chambers by means of dry heat or superheated steam. Mattresses and cushions must be laid open for disinfection in this way. The sick-room should afterwards be disinfected by fumigation with mercuric chloride, chlorine gas, or sulphurous acid gas, doors and windows being kept tightly closed for at least twelve hours. Free ventilation should complete the process of disinfection.

König, of Göttingen, in an article on the disinfection of sleeping-apartments in the *Centralblatt für Chirurgie* (1897), recommends the following procedure as simple and effectual. From one and a half to two ounces of mercuric chloride (corrosive sublimate) is put on a plate over a chafing-dish in the centre of the apartment. The windows and doors of the room are then closed. At the expiration of three or four hours the windows are opened, and the apartment is thoroughly aired. The person entering the room should take the precaution to hold a moist sponge or a damp cloth over the mouth and nose in order not to inhale the mercurial vapor. The following day the windows are again closed and some sulphur is burned in order to neutralize any of the mercurial fumes which may linger about the furniture and other articles in the room. After a final airing and cleaning, the apartment may be reoccupied without risk of infection.

Since he has adopted this method of disinfection, König has never seen a second case of contagious disease attributable to infection remaining in the sick-room.

A convenient, though rather costly, method of disinfection is by the use of thiocamf. This new and powerful disinfectant was first described in 1890 by Dr. J. Emerson Reynolds, Professor of Chemistry in the University of Dublin. Thiocamf is a liquid combination of sulphur dioxide, camphor, and various volatile aromatic bodies. It possesses the remarkable property of giving off a very large volume of effective germicides on mere exposure to the atmosphere, and can be advantageously used for disinfecting an apartment. The air of the closed room is first moistened by sprinkling hot water freely about; a sufficient quantity of thiocamf is then poured on a large flat dish or old tray, and the place is shut up for two days. The usual thorough cleansing and ventilation of the apartment should afterwards take place. About six fluidounces of thiocamf are required for a small bed-room, and double that amount if the room be large.

Increasing the Power of Resistance.—Regarding the introduction

into the body of the specific virus, or morbific agent, of smallpox as in each case the *exciting cause* of the specific disease in question, we find that certain *predisposing causes* usually coexist when an individual contracts that disease. There must be, in addition to the infection, a predisposition to the disease. The chief predisponents of febrile disorders, including smallpox, are the presence of an antecedent disease, the introduction into the body of putrescent organic matter in food, water, or air; and excessive generation of effete matter within the body, as during the puerperal state, after severe surgical injuries or operations, or even consequent upon overexertion of mind or body. Overcrowding and defective ventilation, alcoholic intemperance, destitution, and deficient alimentation are also powerful predisponents.

To counteract these predisponents in an individual who is exposed or is likely to be exposed to the poison of smallpox, the following preventive measures should be adopted. Close attention must be paid to the general health. Wholesome, plain food, an abundant supply of pure water, and fresh air should be at the disposal of every man, woman, and child. Strict sanitary precautions should be taken in the case of a parturient or pregnant woman, and of an injured or wounded person. "Fatigue of mind or of body is to be scrupulously shunned," says Murchison, when speaking of persons exposed to the poison of typhus, but his words are equally true as regards smallpox. Sufficient cubic air space and free ventilation in the dwelling are essential to health. The vice of alcoholic intemperance both betrays and kills. It is not so widely known as it should be that this deadly sin—*deadly* not less in a physical than in a moral sense—not only strongly predisposes to smallpox among other infectious diseases, but also materially lessens the chance of recovery from it. "The prevention of scarcity of food, loss of employment, and other causes of destitution," writes Murchison, "is not always within human power; but, under such circumstances, every means, both public and private, calculated to alleviate the distresses of the poor should be adopted."

Quarantine.—The third great means at our disposal in the attempt to check the spread of one of the infectious fevers, such as smallpox, is the strict enforcement of quarantine (using the term in its modern acceptation, as defined above) and of isolation.

In private families, occupying an entire house, it will suffice to keep apart from the rest of the household any member suspected to have contracted smallpox until the incubation period of twelve days has passed by without the development of suspicious symptoms. Where a number of families dwell under one roof in a crowded city

tenement house, "refuges" should be provided for persons removed from the infected house. The sick should be at once removed to hospital. The refuges should be arranged in sets of rooms or *flats*—so that each family might keep together. Their removal to such a refuge would permit of the convenient cleansing and disinfection of the infected house.

A member of a private family actually, or suspected to be, suffering under an infectious or "taking" disease like smallpox, should be at once *isolated*, preferably in a separate building, but failing this in an airy room at the top of the house. A sheet should be hung outside the door of this room, reaching to the floor and kept saturated with some liquid volatile disinfectant, like carbolic acid, sanitas, or chloride of lime. All fomites, or carriers of infection, should, as far as possible, be removed from the sick-chamber—for example, bed-curtains, carpets, and non-essential articles of furniture. The hygiene of the sick-room should be rigorously attended to.

Among the poorer classes isolation is with difficulty carried out. The means to be employed for the purpose are: (1) the early removal of the smallpox patient to a suitably constructed epidemic hospital in an open space—the removal to be made in a properly equipped ambulance; (2) his admission, first to a reception-room, where his own clothes should be taken off and where he should be washed and made tidy before he is placed in bed in a suitable airy well-ventilated and properly heated ward, the windows being either filled in with panes of red glass or fitted with red curtains for a reason to be afterwards explained (p. 475); (3) his treatment in such a ward, reserved for smallpox cases only, and to which visitors should not have access except under the most pressing and urgent circumstances; and (4) lastly, his removal in due time to a convalescent home for infectious diseases. Permanent epidemic hospitals and convalescent homes should be provided by every sanitary authority, separate blocks being reserved for, or (should the occasion arise) appropriated to, the reception and treatment of smallpox. The accommodation in such hospitals and homes ought to be at the rate of one bed for every two hundred of an urban population, and every four hundred of a rural population.

The preventive measures which call for remark in reference to the management and control of smallpox are: (1) isolation of the sick; (2) inoculation; (3) vaccination.

Isolation.—Of these topics, the first has just been discussed under the two headings of quarantine and isolation. It will be sufficient, therefore, to repeat that isolation consists in the removal of the sick

to suitable epidemic hospitals, the providing of refuges for the inhabitants of infected tenement houses or other dwellings, efficient disinfection, and the establishment of convalescent homes.

It may be well to specify the duration of quarantine in the case of smallpox as eighteen days, and of isolation (as less definitely) until every scab or scale has fallen off.

Inoculation.—As regards inoculation, the intention was to engraft, by means of an *attenuated virus* of the disease, a mild form of smallpox on a healthy individual, whose receptivity or susceptibility might be supposed to be slight or low in consequence of his existing good health. The disadvantages of this procedure were that it gave smallpox to many who would otherwise have, perhaps, escaped the disease altogether, while it was impossible to guarantee that the resulting attack of smallpox would be mild.

In 1840 an Act of Parliament was passed rendering smallpox inoculation unlawful in England (3 and 4 Vict., cap. 29).

Inoculation was declared to be illegal in Ireland by the fourth section of the "Vaccination Amendment (Ireland) Act" of 1868 (31 and 32 Vict., cap. 87).

The operation had been practised from time immemorial in China and also in Persia. The Chinese plan of giving smallpox to persons in health consisted in inserting into the nostrils tents of charpie covered with the dried crusts of the variolous eruption. They called the procedure "sowing the smallpox." From China and Persia inoculation or "engrafting" was introduced into Georgia, Circassia, Turkey, and Greece. In 1717 a very clever English woman, by name Lady Mary Wortley Montague, wife of the British Ambassador at the Ottoman Court, wrote home glowing accounts of the marvellous results of inoculation as practised at Adrianople, among other persons upon her own son, a boy six years of age. Her influence led to the open adoption of the procedure in England in April, 1721, and two years later, in 1723, Dr. Bryan Robinson, sometime President of the King and Queen's College of Physicians, first performed the operation in Ireland. Many years elapsed before it obtained a footing in France, where at first it had been rigorously prohibited by law; but in 1756 the children of the Duke of Orleans were inoculated, and in 1758 the practice was introduced into most of the large towns.

A favorite analogous procedure, practised since the last century by Continental veterinary surgeons and farmers, was called clavelization—a term derived from *clavelée*, the French name for smallpox of sheep (*Variolæ ovinæ*), a disease popularly known in England as "tag-sore," or "sheep-rot"; in Italy as "vaccuolo."

The object of clavelization was by repeated inoculations to attenuate the virus of sheeppox. And exactly in the same way it was sought, by employing virus from a discrete case of smallpox which had been modified by antecedent inoculation, to communicate a very mild variola.

The operation (according to Trousseau) consisted in raising the epidermis by means of a lancet charged with such an attenuated virus or lymph. A mere prick was sufficient. The resulting symptoms were, first *local*, then *constitutional*. Thus, on the second day after inoculation, a small red pimple appeared at the site of puncture; by the fifth day this had become a conical vesicle (sometimes umbilicated); on the seventh day, the vesicle had developed into a pustule, surrounded by a slightly red inflammatory areola, which gradually increased up to the ninth or tenth day, when a ring of secondary small pustules, true satellites of the first, formed upon the inflammatory areola. This pustule of inoculation resembled a kind of large pock which is sometimes found in natural smallpox, and to which Van Swieten, of Vienna, gave the name of *Meisterpocken*, masterpock, or what Trousseau called *le maître bouton*.

On the ninth or tenth day after inoculation the constitutional symptoms used to make their appearance. They were, in a word, all the primary or prodromal symptoms of smallpox. Finally, about the eleventh, twelfth, or thirteenth day, the specific eruption was seen—in general but slightly confluent, following the course of ordinary or sometimes that of modified smallpox.

I have given Trousseau's account of the phenomena attending inoculation at this length because those phenomena are exactly analogous to the features presented after successful vaccination.

Vaccination (Germ., *Kuhpockenimpfung*).—About the middle of the eighteenth century the opinion gained ground in England that inoculation with cowpox lymph protected from smallpox.

E. Crookshank, in his elaborate "History and Pathology of Vaccination," says: "In some parts of the country a belief existed among those who had the care of cattle that a disease of cows, which they called 'cowpox,' when communicated to the milkers, afforded them protection from smallpox." It is necessary to explain that various domestic animals are liable to a disease which is practically smallpox. Thus, a variety of the "grease" (Fr., *eaux aux jambes*) of horses —in which an eruption appears usually on the foot-joints—is properly called Variolæ equinæ. The "tag-sore" (Fr., *clavelée*) of sheep is Variolæ ovinæ; and the well-known "cowpox," in which the eruption is almost exclusively observed upon the udder and teats of

the cow, is technically called Variolæ vaccinæ (Fr., *picote*), or, shortly, Vaccina (the form Vaccinia is etymologically incorrect).

At a time when the majority of the people were deeply pitted with smallpox, the immunity enjoyed by the comely milkmaids of Gloucestershire and Devonshire from the unsightly scars left by the disease could not fail to attract attention. It was noticed that the dairy maids and farm laborers were subject to an attack of sores on their hands, which seemed to arise from contact with pustules on the udders of milch cows. Those who suffered from this apparently local malady of sore hands were observed to escape smallpox. At length, in 1774, Benjamin Jesty, a Gloucestershire farmer, who, however, had been born at Yetminster, in Dorsetshire, became so convinced of the protective efficacy of cowpox against smallpox that he inoculated his wife and two sons with cowpox—thus performing vaccination for the first time, and anticipating Edward Jenner by no fewer than twenty-two years. On May 14th, 1796, Jenner vaccinated a peasant lad, whom he failed to inoculate with smallpox two months afterwards. The crucial test was in this way applied to the efficacy of vaccination as a preventive measure.

It would be foreign to our present purpose to linger over the history of vaccination; nor is it necessary at this time of day to take much trouble to refute the views of the fanatical "anti-vaccination" party. Before the introduction of vaccination, the annual mortality from smallpox in England and Wales alone was at the rate of 3,000 deaths in every million of the population—this, according to the census of 1891, would correspond to a loss of some 87,000 lives per annum—the population of England and Wales being 29,081,047 in April of that year. In 1890 smallpox caused only 15 deaths in England; and the average annual number of deaths from this disease in the ten years 1881–90 inclusive, was 1,227.8—that is, one-seventieth part only of the death-rate of pre-vaccination times.

But vaccination has not only diminished the number of cases of smallpox, it is also found to influence the death-rate among those attacked to a very remarkable extent. In Sheffield, in the outbreak of 1887–88, of 4,151 vaccinated patients, 200 died, or 4.8 per cent.; of 552 unvaccinated patients, 274 died, or 49.6 per cent.

The following tables are taken from a report on the epidemic of 1871–72, as observed in Cork Street Fever Hospital, Dublin, by Dr. T. W. Grimshaw, C.B., now Registrar-General for Ireland and consulting physician to the hospital [49] (in table VII. the statistics are those of Cork Street Fever Hospital):

TABLE VI.

Hospitals.	Mortality Per Cent.		
	Vaccinated.	Unvaccinated.	General.
Cork Street	10.8	71.8	21.7
Hardwicke	11.2	78.57	20.0
Cork	5.5	58.0	22.5
London Smallpox	14.9	66.2	18.8
Hampstead (London)	11.4	51.2	19.36
Homerton	5.9	37.7	16.3

TABLE VII.

	Discrete.			Confluent.			Malignant.			Total.		
	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.
Vaccinated	443	1	0.2	143	46	32.3	25	18	71.8	611	65	10.8
Unvaccinated.	17	6	35.1	94	67	71.2	24	24	100.0	135	97	71.8
Total	460	7	1.6	237	113	47.6	49	42	85.7	746	162	21.6
Per cent. vaccinated in each class.	96.3			60.4			51.9			81.8		

Of the vaccinated cases in the discrete variety, the mortality was practically nothing (0.2 per cent.), only one patient having died. In that case the patient had inflammation of the lungs, probably quite independent of the smallpox. Of the unvaccinated patients, however, in this class, 35.1 per cent. died. In the confluent cases the mortality among the vaccinated patients was 32.3 per cent., while among the unvaccinated it was as high as 71.2 per cent. In the malignant or purpuric variety, the mortality among the vaccinated patients was 71.8 per cent., or about the same as among the unvaccinated confluent cases, while in this variety *not one* unvaccinated case recovered. It may be merely a coincidence of percentage mortality; but it is a remarkable fact that in the cases under consideration vaccination reduced the mortality of confluent cases to that of discrete unvaccinated cases, and that of malignant to that of confluent unvaccinated cases. The proportion of vaccinated to unvaccinated cases in each variety is considerably greater, except in the malignant form, where the proportions are nearly equal. The difference is most remarkable in the discrete variety, where the number of unvaccinated cases is very small—in other words, vaccination *prevented* a large number of these cases from being confluent.

In my "Medical Report of the Fever Hospital and House of Recovery, Cork Street, Dublin," for the year ended March 31st, 1881, I give an account of the still more terrible epidemic of 1876–1881, proceeding on very much the same lines as Dr. Grimshaw's report. The number of cases with which my report deals is so large—namely, 2,815 from April 1st, 1876, to March 31st, 1881—that the results may fairly be considered conclusive as to the modifying influence of vaccination over (1) the type of the disease, and (2) its fatality.

TABLE VIII.—SHOWING THE RELATION BETWEEN VACCINATION AND THE PREVALENCE AND SEVERITY OF SMALLPOX.

From April 1st, 1876, to March 31st, 1881.

	DISCRETE.			CONFLUENT.			MALIGNANT.			TOTAL.		
	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.	Total.	Died.	Mortality per cent.
Vaccinated.....	1,539	13	0.8	552	127	23.0	212	146	68.9	2,303	286	12.4
Unvaccinated.....	86	1	1.1	305	217	71.1	121	107	88.4	512	325	63.5
Total..	1,625	14	.86	857	344	40.1	333	253	76 0	2,815	611	21.7
Per cent. vaccinated in each class.	94.7			64.4			63.7			81.8		

Of 1,625 patients who suffered from discrete smallpox, 1,539 were vaccinated, and only 86 were unvaccinated—the percentage of those vaccinated being 94.7. There were 14 deaths—the rate of mortality being 0.86 per cent. Among these 14 deaths was that of an infant of nine months, who had not been vaccinated. At least half the victims (7) succumbed to the complications of discrete smallpox, dying *in* or *after*, not *of*, this disease.

Of 857 patients suffering from confluent smallpox, 552 had been vaccinated and 305 were unvaccinated—that is, 64.4 only out of every 100 patients had been vaccinated. There were 344 deaths, the rate of mortality being 40.1 per cent. But of the vaccinated cases only 23 per cent. died, compared with 71.1 per cent. of the unvaccinated.

Of 333 malignant cases, 212 had been vaccinated, or 63.7 per cent., and 121 were unvaccinated. The deaths numbered 253, the mortality being at the rate of 76 per cent. Of the vaccinated patients 68.9 per cent. died, but of the unvaccinated 88.4 per cent. died.

Of the 2,815 patients in all who were treated, 2,303, or 81.8 per cent., had been vaccinated and 512 had not been vaccinated. There were 611 deaths, or a mortality of 21.7 per cent. Among the vaccinated 286 deaths occurred, the mortality falling to 12.4 per cent.

Among the unvaccinated 325 deaths took place, the mortality rising to 63.5 per cent.

In very few instances, indeed, had the patients been revaccinated, probably in not more than 10 out of the whole 2,815 cases.

It will be seen then from Table VIII. that from April 1st, 1876, to March 31, 1881, the percentage mortality was 12.4 among those patients who had been vaccinated at least once in their lifetime, but as high as 63.4 among the unfortunates who had never been vaccinated. Of every 100 patients who had discrete smallpox, 94.7 were vaccinated; of every 100 patients who had confluent smallpox, 64.4 were vaccinated; of every 100 patients who had malignant smallpox, 63.7 were vaccinated. Of every 100 patients admitted in the whole period embraced in the table, 81.8 had been vaccinated.

To those who believe that vaccination is a certain preventive against smallpox, these facts must prove sufficiently startling. To the opponents of vaccination they may furnish an argument which is at best, however, only fallacious. If we calmly and dispassionately reflect on the matter, we must come to these conclusions: first, that vaccination, like a previous attack of smallpox itself, is only a *temporary and therefore imperfect preventive* against smallpox; secondly, that the operation should be repeated *at least once* in a lifetime to keep up its protective efficacy; thirdly, that there can be no doubt as to the lessening of the severity and fatality of smallpox due to even one vaccination.

Many years ago Mr. Marson, of the Smallpox Hospital, London, showed as a result of his examination of 5,000 cases, between 1836 and 1855, that the number of vaccinal cicatrices seems to influence the mortality from smallpox. The death-rate among patients having only one cicatrix was 7.73 per cent.; that among those who had two cicatrices was 4.7; that in the presence of three cicatrices was 1.95, and that with four or more cicatrices was only 0.55 per cent.

Very similar results to these were obtained by the Royal Commission on Vaccination, which reported in 1896. The statistics submitted to that commission show that of the fatal cases of smallpox among the vaccinated in recent outbreaks: 7.6 per cent. had only one vaccination mark; 7.0 per cent. had two marks; 4.2 per cent. had three marks; 2.4 per cent. had four marks (Sec. 293).

There can be no doubt that the protective efficacy of vaccination wears out gradually with the lapse of time. Periodical revaccination every seven or ten years is, therefore, necessary if smallpox is to be completely prevented, any case in which revaccination at stated intervals has failed being always of a most peculiar nature.

S. Coupland [50] has published elaborate statistics from recent epi-

demics at Gloucester, Leicester, and Dewsbury, showing that: (1) where the child population is largely unvaccinated, the attacks and mortality are highest in the earliest years of life; (2) that the mean attack rate is found between ten and thirty years, but that here the fatality of the attacks is least; (3) that above thirty the lowest rate of attacks is found with a rather higher fatality; (4) that vaccination reduces the incidence of attacks and the fatal results, though in a less degree as age advances; (5) that, though epidemics vary in virulence, the rates are always higher in the unvaccinated than in the vaccinated; (6) the confluent and discrete types of the disease frequently abort in the vaccinated, and severe types are comparatively rare.

On May 29th, 1889, the Royal Commission on Vaccination, just referred to, was appointed by Her Majesty Queen Victoria. The commissioners included well-known public men of varying opinions, the members belonging to the medical profession being Sir James Paget, Bart., Surgeon-General Sir W. Guyer Hunter, K.C.M.G., Sir William Savory, Bart., Dr. J. S. Bristowe, Professor Michael Foster, and Mr. Jonathan Hutchinson. The scope of the inquiry to be made by the commission was thus defined:

1. The effect of vaccination in reducing the prevalence of and mortality from smallpox.

2. What means other than vaccination can be used for diminishing the prevalence of smallpox, and how far such means could be relied on in place of vaccination.

3. The objections made to vaccination on the ground of injurious effects alleged to result therefrom, and the nature and extent of any injurious effects which do in fact result.

4. Whether any, and if so what, means should be adopted for preventing or lessening the ill effects, if any, resulting from vaccination; and whether, and if so by what means, vaccination with animal vaccine should be further facilitated as a part of public vaccination.

5. Whether any alterations should be made in the arrangements and proceedings for securing the performance of vaccination, and, in particular, in the provisions of the Vaccination Acts with respect to prosecutions for non-compliance with the law.

The report of the Commission was issued in 1896. It is a voluminous document, the result of seven years' work. The Commission held one hundred and thirty-six meetings, examined one hundred and eighty-seven witnesses, and investigated six epidemics which had within recent years prevailed at Gloucester, Sheffield, Warrington, Dewsbury, Leicester, and in London.

In Gloucester and Leicester the practice of vaccination had, to a large extent, been abandoned for some years prior to the outbreaks

in those towns. In Leicester the percentage of births unaccounted for by the vaccinating officers, in 1892, was 80.1. In Gloucester, in 1894, it was 85 per cent. In Leicester the percentage of total smallpox deaths which occurred under ten years of age was 71.4, in Gloucester 64.5. At Gloucester, 26 vaccinated children under ten years were attacked, of whom, 1, or 3.8 per cent. died. Of unvaccinated children of like age, 680 were attacked, of whom 279, or 41 per cent. died.

With regard to "the effect of vaccination in reducing the prevalence of and mortality from smallpox," the Commission having reviewed the evidence, find that:

1. It diminishes the liability to be attacked by the disease.

2. It modifies the character of the disease, and renders it (*a*) less fatal and (*b*) of a milder and less severe type.

3. The protection it affords against attacks of the disease is greatest during the years immediately succeeding the operation of vaccination. It is impossible to fix with precision the length of this period of highest protection. Though not in all cases the same, if a period is to be fixed, it might fairly be said to cover in general a period of nine or ten years.

4. After the lapse of the period of highest protective potency, the efficacy of vaccination to protect against attack rapidly diminishes, but it is still considerable in the next quinquennium, and possibly never altogether ceases.

5. Power to modify the character of the disease is also greatest in the period in which its power to protect is greatest, but its power thus to modify the disease does not diminish as rapidly as its protective influence against attacks, and its efficacy during the later periods of life to modify the disease is still considerable.

6. Revaccination restores the protection which lapse of time has diminished, but the evidence shows that this protection again diminishes, and that to insure the highest degree of protection which vaccination can give, the operation should be repeated at intervals.

7. The beneficial effects of vaccination are most experienced by those in whose case it has been most thorough. The Commissioners think it may be fairly concluded that when the vaccine matter is inserted in three or four places it is more effectual than when inserted in one or two places only, and that if vaccination marks are of an area of half a square inch, they indicate a better state of protection than if their area be in all considerably below this (Sec. 377).

The *Lancet*, February 20th, 1897, in a leading article on the Report of the Royal Commission, agrees with Noel Humphreys that if there is to be any relaxation of primary vaccination, we must have revacci-

nation made at least equally compulsory. If a conscience clause is admitted, then protection must be made complete by revaccination after ten years for those vaccinated in infancy. Still more is this necessary if official vaccinators are abolished, and a crop of one-mark vaccinees grows up. F. T. Bond urges, in addition, that efficient primary vaccination should be compulsory at the beginning of school life, while the conscience clause should be limited to the case of infants.

That vaccination has in rare instances done harm cannot be disputed. Unsuitable subjects have been vaccinated, or the lymph has been taken from improper sources; but such mishaps afford no valid argument against the practice of vaccination, however much they may lead us to call in question the skill and care of the operator in each untoward case.

The circumstances which conduce to the success of the operation are briefly the following:

1. The subject to be vaccinated should be healthy. Special provision is made in the Vaccination Act for postponing the operation if the individual is not quite well. The presence of skin diseases and the propinquity of scarlet fever or erysipelas forbid the operation.

The periods of teething and of weaning should be avoided for the performance of vaccination.

2. The vaccinifer should also be healthy, vaccinated for the first time, and, above all, free from any syphilitic taint. The best age is as soon after two months as possible; but vaccination may be, and, in epidemic times, regardless of age or any other circumstances, should be performed much earlier. In 1878, smallpox raging at the time, I vaccinated one of my own children at the age of three weeks successfully and without any untoward result.

3. The lymph should be taken between the fifth and eighth days. As a French medical poet, Casimir Delavigne by name, quoted by Trousseau, sings

> "Puisez le germe heureux dans sa fraîcheur première
> Quand le soleil cinq fois a fourni sa carrière."

> "Draw forth the auspicious germ in its first freshness,
> When the sun has five times completed his course."

The eighth day, inclusive, is generally selected in the United Kingdom as that of inspection.

4. The incisions, or scarifications, should not penetrate to the subcutaneous areolar tissue. They should be made with a scrupulously clean instrument, sterilized before and after operation with absolute alcohol and dipped in sterilized water.

5. Bleeding should be avoided as much as possible, lest the lymph should be washed away from the site of inoculation. Blood should not be drawn when piercing the vesicle to obtain the lymph.

6. Jenner's "golden rule" should always be observed, and that is—not to use lymph from a vesicle which has already showed the "areola," or inflammatory ring which forms around the vaccine vesicle at the beginning of the second week.

7. A thin, serous, readily flowing lymph should not be used. Good lymph is perfectly limpid and viscid or sticky.

Whenever practicable, the lymph, which may be bovine or humanized (that is, derived from the heifer or from a human being already vaccinated, but not revaccinated) should be carried directly from arm to arm. This, however, is often impossible, and so the lymph must be preserved for future uses. The old-fashioned method was to allow the lymph to dry in a thin film on flat ivory or bone points. A much better plan is to preserve the lymph in hermetically sealed capillary glass tubes. Dr. Alexander Nixon Montgomery, Secretary of the Vaccine Department of the Local Government Board for Ireland, prefers points if wrapped in tinfoil, and if care is taken, when using them, to quite remove the vaccine from the points. Müller, of Berlin, usually mixes the lymph carefully with two parts of glycerin and two parts of distilled water (by means of a small brush) in a watch-glass, and preserves this diluted vaccine lymph in air-tight capillary tubes. He holds that the activity of the lymph is not impaired by this procedure, and the precious virus is economized. Dr. Montgomery, on the contrary, is of opinion that vaccine in capillary tubes should not be mixed with anything.

Vaccination is generally done upon the outside of the left arm, about the insertion of the deltoid muscle. From an æsthetic point of view, care should be taken to vaccinate girls at some place where the scars will be as far as possible hidden by the future evening dress. For this purpose, some prefer to have vaccination done upon the leg in accordance with the fashion which prevails in Germany. At least four sets of minute punctures or scarifications are made with a vaccinating needle or lancet, moistened or "armed" with the vaccine lymph, above and below the insertion of the deltoid muscle. A little of the lymph should afterwards be rubbed into the punctures. The four insertions should be made so that the combined area of vesication on the eighth day shall cover a skin surface of at least half a square inch in the case of each of the four groups of vesicles.

Various instruments for vaccination have been designed, one of the neatest and best being Rose's "vaccinator." This ingenious little instrument consists of a smooth blade at one end and a series of five

needles, the centre one slightly larger than the rest, at the other end. When vaccinating, the operator should project the needles the required length by pressing down the cap. He should then press the vaccinator on the skin and rotate it once, so as to produce a circular scratch. The lymph can then be well rubbed in from the surface of the blunt end which has been loaded from a fresh vesicle.

According to Hebra, the most satisfactory instrument is a lancet having one convex surface, the other hollowed and presenting a groove to which a drop of the lymph adheres. A. Nixon Montgomery considers that a lancet, smooth on both sides, is the best, as it can be most readily sterilized.

Another instrument, called by the Germans *Impffeder*, or vaccine pen, resembles a drawing pen, and consists of two parallel limbs with cutting extremities, between which the lymph is taken up by capillary attraction. In employing this instrument the vaccine matter is introduced beneath the cuticle by a horizontal or vertical incision (Hebra).

Another method, not used in Ireland, is by multiple punctures for which a special small lancet is required. Montgomery, however, thinks that fine parallel scratches crossed, made with an ordinary vaccination lancet, are the best form of vaccination for adults, while Rose's instrument should be employed for arm-to-arm vaccination in the case of infants.

Vaccina.—The symptoms of this affection are first local and then constitutional—the latter in most cases being very slightly marked. On the third day (inclusive) a patch of redness at the site of vaccination appears and rapidly develops into a papule or pimple, which in its turn, about the fifth day, becomes surmounted with a pearly vesicle, multilocular, oval or circular in outline, with raised margin and depressed centre. This vesicle enlarges, while its contents also increase—remaining, however, clear as crystal—until the eighth day, when it attains its perfect growth. An inflammatory red zone, called the "areola," now develops, beginning round the base of the vesicle and thence spreading out, perhaps to a distance of two or three inches. After the tenth day the areola fades, and the vesicle begins to shrink and dry up in the centre. The contained lymph becomes opaque and thickens. A vaccine vesicle never should contain pus. Hence the term "vaccine pustule," sometimes used, is very misleading. If pus is present, it shows that the vesicle has been rubbed and the staphylococcus pyogenes aureus, or some other pus-producing microbe, has effected an entrance. By the fourteenth or fifteenth day a hard, dry, brown scab forms, which finally separates and falls off about the twenty-first day. A circular, slightly depressed, foveate

(or pitted), cicatrix remains, which—except in rare instances—is permanent through after-life.

During the earlier stages, the vaccine vesicles should be relieved from any pressure or friction, which might increase inflammatory action, but on no account should a vaccine shield, or protector of any kind, be used to protect the vesicles. In all cases the vaccinated person should be seen on the eighth day—the day week—from the operation, when a certificate of successful vaccination may be given if the vesicle is well formed and running a natural course.

The constitutional symptoms are: Slight pyrexia from the fourth day, becoming more marked from the eighth to the tenth days; often derangement of the stomach and bowels during the stage of areola, with restlessness. The axillary glands may also swell, and rashes may show upon the skin—either a blush (*vaccinal roseola*), or a crop of papules (*vaccinal lichen*), or a vesicular rash (*vaccinal herpes*). In normal cases all these symptoms subside in a few days, or they may fail to appear at all.

Sir Thomas Watson says that a very ingenious test, free from all ambiguity, by which we determine whether the cowpox is running its proper course or not, was devised by Mr. Bryce—hence called "Bryce's test." His plan was this: He vaccinated the other arm, or some other part of the body four or five days after the first vaccination. If the system had been properly affected by the first operation, the inflammation of the second vesicle would proceed so much more rapidly than usual that it would be at its height and would decline and disappear as early as that of the first: only the vesicle and its areola would be smaller. One of the earliest disciples of Dr. Jenner, Mr. Hicks, used in a doubtful case to repeat vaccination in a few days after the first operation, and he remarked that the second vesicle made "immense strides to overtake the first."

Vaccino-Syphilis.—The inoculation of the syphilitic virus along with vaccine at the time of vaccination is, in the words of Shelly, "the most lamentable accident by which carelessness or misfortune can prejudice the performance of vaccination." Since the incubation period of syphilis—namely, from three to five weeks—is much longer than that of vaccina, the latter affection usually runs its course before the local inflammation which constitutes a specific chancre begins. This is attended by the usual glandular enlargement (*axillary bubo*) and is followed in due course by the recognized secondary symptoms of constitutional syphilitic infection.

Vaccino-Leprosy.—In a paper read before the Seventh International Congress of Hygiene and Demography, held in London in 1891, Phineas S. Abraham[51] brings forward all the available evidence which

bears on the alleged connection of vaccination with leprosy. He believes that, although we may admit *a priori* the possibility of an occasional accidental inoculation of leprosy by vaccination, we have up to 1891 (when he wrote) no absolutely clear and incontrovertible evidence causally connecting vaccination with leprosy. In his opinion, "any one who says that vaccination is to any extent responsible for the spread of leprosy, talks arrant nonsense." At the same time, in a country where leprosy is rife, Abraham thinks that it will be advisable to exercise particular caution, and if possible avoid, as is now being done in Hawaii, an indiscriminate arm-to-arm vaccination among the natives.

Hansen, of Bergen, informed Abraham that vaccination, which has been compulsory in Norway for many years, has been largely practised in the leprous districts from arm-to-arm and that no case of transferring leprosy thereby has been known. The late Beaven Rake, formerly superintendent of the Trinidad Leper Asylum and also a member of the Indian Leprosy Commission, and George Alfred Buckmaster, vaccinated eighty-seven cases of leprosy at Almora, capital of Kumaon, Northwest Provinces of India. Forty of these developed vesicles, thirty-one being normal. In no case were leprosy bacilli undoubtedly found. The whole question is discussed,[52] and the authors conclude that "it is evident that the risk of transmission of leprosy by vaccination is so small that for all practical purposes it may be disregarded."

Curative Treatment.

This superscription is in one sense somewhat misleading. No physician has ever yet *cured* a case of smallpox. No specific for the disease or for its complications and sequelæ has as yet been discovered. Accordingly we must be content to set before us two great principles of treatment: first, to guide the essential disorder to a favorable termination; and, in the next place, to combat secondary affections as they arise.

There can be no doubt that the mortality from smallpox was enormously increased during the Middle Ages by mistaken and ignorant treatment. The old physicians did all they could to protect the patient from cold and to promote a copious eruption, adopting the vulgar maxim: "it was better out than in." In the fourteenth century flourished John of Gaddesden, author of a curious book entitled "Rosa Anglica," court physician of the day, but "a very sad knave," as Sir Thomas Watson calls him. This representative physician of the age not only put the unhappy smallpox patient on a

"hot regimen," administering wine and cordials, piling on bedclothes, and jealously excluding every breath of fresh air from the sick-room, but surrounded the half-suffocated victim with red curtains, red walls, and red furniture of all kinds—for in this color there was, he averred, a peculiar virtue.

To the celebrated Thomas Sydenham, who lived in the seventeenth century, belongs the credit of substituting for this barbarous and disastrous system of treatment the opposite or "cooling regimen" in smallpox, and this practice is pursued to the present day with the happiest results.

So far, however, as the treatment of smallpox by red light is concerned, after the lapse of five centuries, the therapeutic skill and clinical acumen of John of Gaddesden are at last vindicated, and with the poet Chaucer we may say:

"For out of the old fieldes, as men saithe,
Cometh all this new corn from yere to yere,
And out of old bookes, in good faithe,
Cometh all this new science that men lere."

The subject has been attracting attention since 1867, when C. Black,[53] of Chesterfield, came to the conclusion that "the complete exclusion of light from the eruption of smallpox in persons unprotected by vaccination effectually prevents pitting of the face."

In 1871 J. H. Waters,[54] of London, published a short paper on the "Action of Light in Smallpox." His observations were apparently made quite independently, and led him to assert that "if white light is entirely excluded from the patient, there is no doubt the disease is less severe; by the white light I mean daylight."

In the same year, W. H. Barlow,[55] of Manchester, bore additional testimony to the usefulness of the exclusion of light in the treatment of small-pox. He recalls an experiment recorded in the *Lancet* of August 24th, 1867, in which part of the face of a smallpox patient was covered with a warm solution of colored gelatin (to exclude the actinic rays), the rest of the features being left exposed to the full action of the light, with the result of showing a marked contrast between the two portions.

Barlow wisely advocates the necessity of exercising care and judgment in the application of the method of treatment by exclusion of light, suggesting that only the actinic rays of the solar prism should be cut off, in order to avoid that depressing effect upon the mind which total darkness would probably cause, and which seems to Barlow to have much to say to the fatal result. Again, "we must not forget that the outward manifestations" of smallpox, which are shown to be controlled by the exclusion of light, "do not form the whole of

the disease, and that, grave as may be the consequences of their unchecked career, there are more serious forces behind, for which these form the outlets, and as it were, the safety-valves of the system."

Gallavardin[56] had during seven years seen marked effects from the treatment of smallpox in the dark, but only when it was thoroughly carried out. Suppuration and pitting were prevented by the treatment.

In a suggestive paper on the effects of light upon the skin, Niels R. Finsen,[57] Prosector of Anatomy, Copenhagen, observes that our knowledge of this subject has greatly increased within recent years. It was formerly supposed that it was the solar heat rays which were especially injurious in the so-called solar eczema, which the name *erythema* or *eczema caloricum* also shows. In the same way pigmentations were supposed to be due to the caloric rays, but to be independent of wind and weather.

From the investigations, especially of Unna,[58] Widmark[59] of Stockholm, and Hammer[60] of Stuttgart, it has, however, been now absolutely determined that it is exclusively the chemical rays in sunlight, especially the ultra-violet rays, which are active in causing both pigmentation and solar eczema. Hammer and Widmark have shown in their papers that precisely the same phenomena may be produced by strong electric light, since this light is particularly rich in chemical rays. Against heat as the active agent the fact, for example, detailed by Widmark about Arctic travellers, and by Hammer about tourists on glaciers, tells in the clearest way. These individuals, even with the temperature below freezing-point, may suffer severely from light erythema, which is due to the strong reflection of the light from the ice fields.

The view that it is the chemical and not the caloric rays which are active, and also that the skin affection induced by strong electric light is identical with solar erythema, was first advanced by Charcot[61] in 1859, but was not proved scientifically until Widmark's experiments in 1889.

The so-called chemical rays, which are essentially situated in the blue and violet, and especially in the ultra-violet, part of the spectrum, are the most refrangible of the rays of light; in this area the chemical activity is strongest, the caloric activity is weakest. The converse holds good in the other end of the spectrum, where are found the red and ultra-red rays which are the least refrangible. Here the caloric activity is greatest and the chemical activity least.

Finsen does not appear to have made a practical trial of the method of treating smallpox suggested by him at the close of his paper—that is, by complete exclusion of daylight or, what would

doubtless have the same effect—by the use of tightly closing red curtains, or windows of red glass. In the number of the *Hospitalstidende* for September 6th, 1893, he writes an interesting letter on the "Treatment of Smallpox," in which he states that in an epidemic which prevailed at Bergen in the summer of 1893 Lindholm, medical officer of health (*Stadsfisikus*), and Svendsen, visiting physician of the Municipal Hospital, had tried his method with gratifying success. In a letter dated August 2d, Lindholm wrote to Finsen as follows: "I have the pleasure to inform you that the proposed treatment of smallpox seems to have an excellent effect, as the œdema quickly subsides and suppurative fever fails to appear." Twenty cases, of which ten were unvaccinated children, were treated by Lindholm[62] in this manner with complete success. All recovered, although severely attacked; in one case even "black smallpox" was present. The eruption dried up shortly after its appearance, no fever of maturation took place, and the patients recovered very soon, having but few scars.

Svendsen published an account of this epidemic in the Bergen *Medicinsk Revue* for October, 1893. He bears eloquent testimony to the efficacy of the treatment of smallpox by exclusion of the chemical rays of light. In his experience the vesicles dried up without becoming purulent; in this way suppurative fever was avoided, so that the disease became less dangerous, less protracted, and less painful owing to the absence of ulceration. Furthermore, pitting did not occur. Svendsen thus expresses himself: "The clinical records of the patients treated according to this plan show the following differences: The suppuration stage—the most dangerous and most troublesome in variola—was slurred over; no rise of temperature, no œdema, and so on, occurred. The patients passed at once from the vesicular stage, which seemed to me somewhat protracted, into that of convalescence, and were saved from the ugly pitting."

Svendsen describes a couple of interesting control experiments which he made. He sent a patient out into the daylight after desiccation had occurred everywhere except on the hands, on which there were still a number of vesicles, with the result that these vesicles passed on into suppuration, and the patient had small, not deep, pits on the back of his hands. A second patient was subjected to the same procedure with a like result.

More recently the method has been tried, with less striking though still encouraging results, by Juhel-Renoy,[63] of Paris. He believes that the mere fact of protecting the patient from the action of the chemical rays of sunlight cannot *prevent* suppuration, but it lessens suppuration—"*c'est un procédé d'atténuation de la suppuration*"—it is capable at all events of rendering the post-variolous scars less

perceptible and less disfiguring. In any case, such a result should not be despised and would certainly be appreciated by the patients. Besides, the treatment is easily carried out. Simple red window curtains suffice to absorb the chemical rays of the solar spectrum.

Lastly, C. Feilberg, senior physician at the Oresund Hospital, Copenhagen, reports[64] the results obtained by him in fourteen cases of smallpox treated by exclusion of the chemical rays of daylight in a sporadic outbreak in Copenhagen, in January and February of the year 1894. His paper is illustrated by two photographs and a series of temperature charts, which certainly show a striking modification of both rash and temperature, even in an elderly patient, vaccinated when a child, and in an unvaccinated girl of six years. Feilberg points out that Finsen based this method on the train of thought that, if the chemical rays (blue and violet) can induce inflammation in *healthy* skin, they are all the more likely to possess the power of acting injuriously on *unhealthy* skin. He is of opinion that we should especially look for such an effect in variola, from the fact that the most numerous and deepest scars are, as a rule, found on the face and hands—that is to say, on the parts most exposed to daylight. We should, therefore, exclude the chemical rays from the sick-room.

As my attention had for some time previously been riveted on this method of treatment, I determined to test it in the case of a medical friend who fell ill of smallpox in September, 1894. On Saturday, September 8th, exactly eleven days before the initial symptoms showed themselves, the physician in question had seen a case of smallpox in the stage of invasion. He continued in attendance until the following Thursday (the 13th) when the case was sent to hospital. There the patient, and also her infant child, died afterwards of the disease. My friend's attack proved to be one of confluent smallpox, which ran a severe course. It happened by chance that a large double window in the sick-room was covered from top to bottom with a deep red thick curtain. This was kept constantly drawn, while another red curtain was hung entirely across the folding doors communicating with a spacious front drawing-room, in which one of the windows was kept widely open both by day and by night. A brisk fire in the grate further secured the freest ventilation in both the sick-room and its antechamber. During the remainder of his illness, the patient repeatedly expressed the comfort which the subdued red light afforded him.

The clinical chart (Fig. 11) shows that a sharp secondary fever followed the remission of temperature observed on the sixth and seventh days. But the thermometer rose only to 103° F. on the evening of the ninth day, thus falling short of the fastigium of the primary fever

by 2.2°. The rash was in places dark, but it never became markedly pustular, although the contents of the vesicles were lactescent and opaque, and showed signs of hemorrhage now and again (*Variolæ hæmorrhagicæ pustulosæ* of Curschmann). The local treatment consisted in the smearing of the face and other parts with carbolized vaseline (2.5 per cent. in strength), followed by free use of boric acid

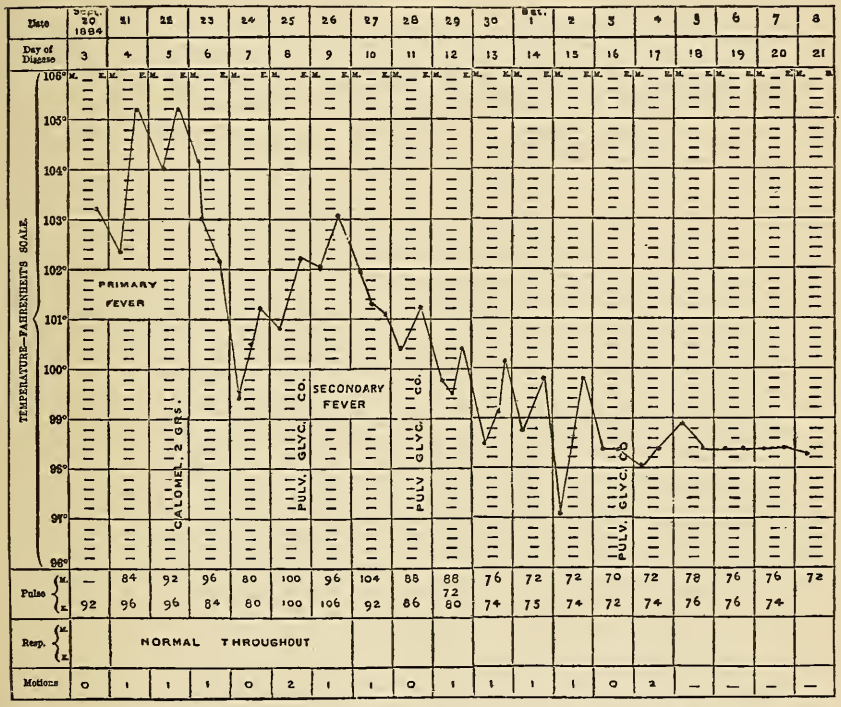

FIG. 11.—Chart Showing the Sharp Rise of the Temperature in the Secondary Fever of Smallpox.

as a dusting powder. Troublesome pruritus about the scrotum was at once relieved by painting over the part with a ten-per-cent. solution of hydrochlorate of cocaine.

In the epidemic of 1894–95 the smallpox patients in Cork Street Hospital, Dublin, were subjected to the red-light method of treatment. John Marshall Day, the resident medical officer, reports that with the use of red blinds eye troubles had ceased to appear, the patients rested well and spoke of the color as soothing. Day is of opinion that pitting is less under this treatment, which also obviates the necessity of applying bandages over the eyes and masks to the face. Pigmentation of the face was lessened. He incidentally mentions

that when the red blinds were kept constantly down, the patients were not nearly so much troubled with flies.

We may with Murchison lay down the following general principles of treatment of smallpox, in common with the other eruptive and continued fevers:

1. To neutralize the fever poison and improve the state of the blood.

2. To promote elimination, not merely of the fever poison, but also of the products of tissue change, or metamorphosis.

3. To reduce temperature and to lessen the frequency of the heart's action.

4. To maintain the nutrition of the body and to stimulate when necessary the heart's action by food and stimulants.

5. To relieve distressing symptoms as they arise, such as headache, sleeplessness, pain, restlessness, prostration, stupor, delirium, cough, constipation, diarrhœa, thirst, and so on.

6. To obviate and counteract local complications, or those secondary affections which intervene in the course of the primary malady, upsetting its normal course and imperilling the patient's life, or prolonging the fever movement to a greater or less extent.

Let us now consider what further measures should be adopted in the management of smallpox under its three chief forms, discrete, confluent, and malignant or hemorrhagic.

Discrete.—Il ne faut que demeurer en repos (Collie). The patient having been placed in bed in a large, airy, and well-ventilated but warm room (55° to 65° F.) should be carefully and skilfully nursed; his hair should be cut close, his hands and face should be washed daily, or twice a day, with warm carbolized water, from one to two per cent. in strength, or with a weak solution of corrosive sublimate (1:2,000). Warm baths are very useful and refreshing. The water may, with advantage, be tinged with permanganate of potassium solution, bearing in mind, however, that this is decolorized at once and rendered inert by soap, or any organic matter, such as sponges, cotton wool, wadding, or flannel. During the pyrexial stage the diet should consist of milk, whey, animal broths, and whipped-up eggs, with or without brandy or whiskey. Fresh fruits are a useful aid where there is constipation, and bananas would seem to be a really valuable food in fever. On the subsidence of the initial pyrexia solid food may be given in small quantities and cautiously—chicken, white fish (which, however, does not always agree), game, or rabbit boiled in milk, are the most suitable dishes at first. Alcoholic stimulants are not generally needed in discrete smallpox, and in any case the greatest care and circumspection should be prac-

tised in prescribing them, particularly for young children and women.

Confluent Smallpox.—The patient should husband his strength by taking to bed at the earliest opportunity and *remaining* there until convalescence has begun—in a word, he must be prevented in every way from exhausting his muscular and nervous powers. The pain in the back may be relieved by dry-cupping, or by the application of an india-rubber bag filled with hot water, or by a hypodermic injection of ergotin. An ice-bag or an evaporating lotion or a hot fomentation applied to the head will often control headache. In all the severer forms of the disease, the patient should not be allowed to assume the upright position for fear of syncope, which is especially likely to come on after a free evacuation of the bowels.

In confluent smallpox the patient is beset by two dangers in particular—general blood-poisoning from the intense and widespread suppuration, and exhaustion from pain, sleeplessness, delirium, and long-continued fever. The food should be both nutritious and digestible, consisting of such articles as milk, eggs, beef-tea, veal broth, chicken broth, mutton broth (strained), meat essences, meat jellies, arrowroot, sago, bread, and milk, custard, tea or coffee, well diluted with milk. If there is a tendency to diarrhœa, the milk should be boiled, or lime water should be given with it, in the proportion of one part in four; or vermicelli, gelatin (isinglass), or arrowroot should be added to the milk or broth. Acids should not be given with milk, which they coagulate or cause to curdle. If the digestive powers are very weak, the food may with advantage be peptonized, the object of which process is to convert insoluble proteids or albuminoids into soluble peptones.

Food should be given at regular intervals—every three hours, every two hours, or even every hour; but, at the same time, the stomach should be allowed to rest for at least the last-named interval, else nausea, vomiting, flatulence, and diarrhœa may be caused through non-assimilation and decomposition of the food.

When a patient remains in a state of stupor he should be roused from time to time to take food; but, if he falls into a tranquil sleep after a period of wakefulness, nervous excitement, or delirium, he should not be aroused merely because the hour for food has come round. In delirious cases, or when the patient is unconscious or unable to swallow, liquid nourishment should be introduced into the stomach by a long tube passed through the nares, or nutrient enemata should be administered. In the latter case the rectum should

first be washed out by an injection of warm water, and then an enema should be given of milk and brandy, or beef-tea, or egg flip, at a suitable temperature (100° F.), and of moderate size (not exceeding four to six ounces). Very few patients can digest more than one pint of animal broth, and from one and a half to two pints of milk, in the twenty-four hours, and these quantities seem to be a fair allowance, under all the circumstances, in the case of an adult.

The question of the administration of alcoholic stimulants in smallpox is an anxious one, and admits of no routine practice. Murchison lays down excellent rules for our guidance. He considers that patients under twenty years of age do best as a rule without any alcohol, whereas most patients over forty are benefited by it after the first week. Intemperate persons require alcohol earlier and in greater quantity than others, and yet it does not always agree. The chief indications for the use of stimulants are derived from the state of the pulse, the heart, the tongue, and the brain, and from the presence of complications, and especially of the "typhoid state" (*i.e.*, stupor, low muttering delirium, tremor, subsultus, involuntary evacuations, coma vigil, etc.).

Alcoholic stimulants are doing a fever patient good if, under their use—

1. The heart's action becomes stronger and less rapid, the impulse increasing in strength and the first sound becoming more distinct;

2. A soft, compressible, undulating, irregular, or intermitting pulse becomes fuller and stronger and more regular in rhythm and volume;

3. A dry, brown tongue becomes clean and moist at the edges;

4. Delirium lessens, the patient becoming more tranquil, or even falling asleep.

Stimulants are more urgently required during the night and in the early morning, when the vital powers are wont to flag. In the forenoon they are less necessary.

In cases of extreme prostration, medicinal stimulants or tonics should be combined with wine or spirits. The preparations and drugs mostly employed under these circumstances are—carbonate of ammonium, the different ethers, sumbul, camphor, musk, turpentine, bark, or quinine.

To check the development of a copious eruption antiseptics have been recommended and tried, but with no striking or even satisfactory results. One of the best and fullest accounts of the antiseptic treatment of smallpox will be found in a paper by my former col-

league, Dr. Arthur Wynne Foot,[65] lately senior physician to the Meath Hospital. The way in which he endeavored to carry out this treatment in the wards of the Meath Hospital during the epidemic of 1871–72 was by giving carbolic acid internally in the shape of the sulphocarbolate of sodium (in doses of from gr. vij. occasionally to gr. lx. in water every third hour), or—when more suitable—the sulphocarbolate of iron; by giving the sulphurous acid of the British Pharmacopœia, diluted with water—one drachm in a wineglassful or two of iced water—as the usual drink; by spraying the larynx with it, and washing the nares and upper surface of the palate with solutions of sulphurous or of carbolic acid; by keeping carbolized oil to the face; by washing the body with solutions of sulphurous acid or of vinegar and water; by throwing pure sulphurous acid about the bed and bed-clothes of the patient; and by burning sulphur in the sick-room.

E. Pepper[66] has called attention to the value of cocaine in smallpox and varioloid. The following is a summary of his conclusions, which were first published in the year 1889. By the use of cocaine, variolous, and *a fortiori* varioloid poisoning, can frequently be arrested in a marked degree. The disorganization of the blood is generally less rapid and less extensive. The fever is less severe and of shorter duration. An incomplete evolution or semi-abortion of the vesicopustules or pustules is of frequent occurrence when cocaine has been regularly employed during the second period of the disease; finally, the various visceral congestions and inflammations are less frequent and less intense. When cocaine is given by the stomach, five drops of a four-per-cent. solution are conveniently administered four times in the twenty-four hours to a child aged five; at the age of ten, ten drops four times in twenty-four hours; and so on, the dose being increased by one drop four times during each twenty-four hours for each year of age; at twenty years of age twenty drops are given four times in the twenty-four hours. Each dose is to be given in a small quantity of water or otherwise according to taste. One-half of these quantities is frequently sufficient. An agreeable mode of giving the drug is in sweetened pastilles, each containing gr. $\frac{1}{2\frac{1}{4}}$ of cocaine, with or without a small quantity of pepsin. Cocaine may also be given in suppositories at intervals of six or eight hours, the quantity thus administered in twenty-four hours never being greater than that given by the mouth. The hypodermic method is not recommended by the author except in the incipient stage when the drug cannot be given by the mouth or the rectum; the dose should be a quarter of that indicated for use by the mouth. The effect of the cocaine must be carefully watched, but the author points out that in variola tolerance of

this drug is strongly marked. This treatment does not exclude the use of other remedies, either general or local, but Pepper says that in many cases in which cocaine is methodically given, little or no further treatment is required. He suggests that during an epidemic of smallpox it would be interesting to study the possible action of the drug as a prophylactic, when given to those particularly exposed to the contagion and to unvaccinated persons. Pepper says the cocaine method of treatment was first introduced by Luton.

My own experience is that in quinine and in perchloride of iron we possess the two most valuable antiseptics for internal use so far as smallpox is concerned. Quinine may be given in five-grain doses thrice daily or oftener. This dose may be administered in water with just enough dilute hydrochloric acid to dissolve it, or with dilute hydrobromic acid and water, or mixed with fresh milk—when three grains of powdered camphor may with advantage be added to each dose.

Other excellent preparations of quinine are the tincture and the ammoniated tincture of the British Pharmacopœia. The former contains one grain of hydrochlorate of quinine in each fluidrachm, the latter a similar quantity of the sulphate in each fluidrachm. Tincture of sumbul, tincture of nux vomica, and spirit of chloroform —ten minims of each—may be prescribed with a drachm of ammoniated tincture of quinine in half a wineglassful of water thrice daily.

Either the tincture or the solution of ferric chloride may be given in twenty to thirty minim doses, with glycerin (℥ ss.) and water (℥ vij.), and perhaps a few minims of liquor strychninæ hydrochloratis. The following prescription will be found useful:

℞ Tinct. ferri perchloridi, ... ℥ ij.
Acid. phosphoric. dil., ... ℥ iss.
Glycerini, ... ℥ iiss.
Tinct. aurantii recentis, ... ℥ ss.
Aquæ chloroformi, ... ad ℥ vi.
M. ft. mistura. Sig. "One-sixth part every sixth hour."

Solution or tincture of acetate of iron may be substituted for the foregoing. These preparations are best taken in water, alone or with small doses of glycerin.

Should it seem desirable to combine quinine and iron, the "ferri et quininæ citras" may be given with spirit of chloroform and infusion of calumba or plain water; or the same scale preparation may be exhibited in five-grain doses in effervescence with granular effervescent citrate of caffeine, or it may be substituted for the ammonio-citrate of iron in the following formula given by William

Whitla, of Belfast, "a most elegant and palatable chalybeate mixture":

℞ Ferri et ammonii citratis, ... gr. cxx.
Acidi citrici, ... gr. cl.
Aquæ destillatæ, ... ad ℥ vi.
Sig. A tablespoonful by measure thrice daily with two tablespoonfuls of the alkaline mixture effervescing.

THE ALKALINE MIXTURE.

℞ Potassii bicarbonatis, ... gr. ccc.
Spiritus chloroformi, ... ℥ ij.
Aquæ, ... ad ℥ xij.
Sig. The alkaline mixture.

If we possessed any certain means of checking the development of a confluent rash in smallpox, much distress and even danger to life in the first instance, and later on permanent disfigurement would be avoided. In a characteristic paper entitled "Some Notes on the Treatment of Smallpox," to which the reader's attention is earnestly directed, William Stokes[67] pointed out that the virulence of the pustulation and the tendency to pitting are directly as the cutaneous vascularity and heat of surface. In proof of this Stokes instanced the case of a strong and healthy young woman, who was admitted to hospital with symptoms of fever, including intense headache. For the relief of this symptom she was leeched freely on the temples. The attack proved to be one of confluent smallpox, but on the face not more than two or three small aborting pustules made their appearance. "Who can doubt," asks Stokes, "that in this instance the depletion of the face influenced the local progress of the disease?" Again, he quotes a case commented on by Graves—that of a man who contracted smallpox while under treatment in one of the surgical wards for a chronic affection of the knee-joint. The affected joint was strapped with mercurial plaster, which exerted such pressure on the neighboring cutaneous capillaries as absolutely to prevent the development of the eruption over the part. In a third case of severe confluent smallpox there was great tumefaction, accompanied with extraordinary heat of the face, and, in the hope of saving the eyes, poultices were applied over them. The patient recovered, but with deep and permanent pitting. There was, however, no pitting on the eyelids or in their immediate neighborhood. From the date of this last case (1849) Stokes adopted as a routine practice the application of light poultices over the entire face, or of a mask of lint steeped in glycerin and water and covered with a corresponding mask of oiled silk. He found that, with but one exception, pitting was effectually

prevented. In that case the patient was delirious, and could not be kept from tearing the poultices off his face.

As the outcome of his observations, Stokes came to the conclusion that, if from an early period we protect the surface from the air and keep it in a permanently moist condition, marking will seldom occur. There are then three important indications of treatment:

1. The exclusion of air.

2. The keeping of the parts in a permanently moist state, so as to prevent the hardening of the scabs.

3. The lessening of the local irritation.

All the authorities are agreed that these indications should be as far as possible fulfilled. Charles West recommends strapping with mercurial plaster or sponging with a solution of corrosive sublimate, apparently attributing a specific action to the mercury in each case. But for this there seems to be no warrant. The late Dr. Alfred Hudson of the Meath Hospital, Dublin, used to smear the face with glycerin. Sir John Banks, Physician to the Hardwicke Fever Hospital, Dublin, many years ago suggested the application of an ointment composed of lapis calaminaris (native impure carbonate of zinc) and glycerin. Dr. Foot applied to the face carbolized oil—varying in strength from 1:4 to 1:8 parts; he also recommended the application of flexible collodion to the papules as early as possible, for its late application only does mischief, forcing the pus to burrow backwards into the cutis, so increasing the dermatitis and insuring pitting. Mr. Marson, of the London Smallpox Hospital, waited until the pustules had burst and the discharge had begun to dry. He then applied the best olive oil, or a mixture of glycerin and rose water in the proportion of 1:3. He also recommended "cold cream," or oxide of zinc ointment, or olive oil and lime water (*linimentum calcis*, or "Carron oil"), or calamine mixed with olive oil. Curschmann speaks highly of the value of cold—even iced—compresses frequently renewed for the relief of pain, swelling, and redness of the skin. The American practice to prevent pitting is exclusion from the room of the solar light and the application of a solution of boric acid (one drachm to one pint of water) by means of compresses, frequently changed, or covered with oiled silk. In Germany a paste—composed of carbolic acid, 4 to 10 parts; olive oil, 40 parts; and prepared chalk, 60 parts—is spread on linen and applied to the parts where the eruption is apt to be worst. This application should be changed every twelve hours.

Dr. Lewentauer[68] suggests the application to the face by means of a mask, and also to the other parts on which the eruption is

marked, of an ointment consisting of salicylic acid, 3 parts; starch, 30 parts; and glycerin, 70 parts.

Bertrand[69] recommends the application, with a brush, as soon as the eruption appears either on the face or in the pharynx of a mixture of 4 gm. (1 drachm) of boric acid to 50 gm. (1½ oz.) of glycerin. The eyes, meanwhile, should be bathed with a tepid saturated solution of boric acid.

Talamon[70] applies ethereal solutions of various antiseptics by means of a spray apparatus. Salol does well only when the rash is slight and scanty; in all cases corrosive sublimate is to be preferred. He sprays the part for a minute three or four times a day—until desiccation takes place—with a solution consisting of corrosive sublimate and citric acid, of each 1 gm. (15.432 grs.), alcohol (90 per cent.) 5 c.c. (80 minims), and ether, sufficient to make 50 c.c. (1½ oz.) The eyes should be guarded during the application.

Skoda prefers compresses moistened with solution of corrosive sublimate (gr. ij.–iv. to water ℥ vi.). Hebra applies only cold-water compresses.

My own plan is to apply over the face a light mask of lint thoroughly soaked in a mixture of iced water and glycerin (a teaspoonful in an ounce of water) and covered with oiled silk.

"Ihle's Paste," which is a mixture of ten grains of resorcin with two drachms each of powdered starch, oxide of zinc, lanolin, and soft paraffin (vaselin) would probably suit some cases. In the earlier stages of the eruption also antiseptic and astringent dusting powders will possibly relieve the distressing heat and irritation of the skin. Boric acid, "dermatol" (subgallate of bismuth), "Emol keleet" (which is a refined fuller's earth), or a carbolized powder like the following, may be recommended:

℞ Acidi carbolici puri liquefacti, ... ℥ ss.
Zinci oxidi, ... ℥ i.
Pulv. lycopodii, ... ℥ i.
Ft. pulvis.

John MacCombie, however, truly says that oils and other preparations often add to the patient's discomfort, and many patients prefer to have no applications whatever on the skin. At the same time he strongly recommends the early separation of the crusts, whether on the face, scalp, or elsewhere. This, he thinks, can best be accomplished by the application of linseed-meal poultices, sprinkled with iodoform. On the face the method most agreeable to the patient is to cut a mask of a single thickness of lint, with apertures for the eyes, nose, and mouth; then to smear a thin layer of linseed-meal

poultice on this, taking care to put on the surface a little vaselin in which iodoform has been mixed (greasy applications do not at this stage—that of decrustation—irritate the patient), and to apply this poultice to the face, changing it at least every two hours. By this means the crusts may be separated more rapidly than by any other.

Closely akin to these va ous measures for lessening the irritation of the surface, keeping the eruption moist, and excluding air, is the treatment of smallpox by the warm or tepid bath.

In his classical "Essay on Fevers," John Huxham advises bathing not only the legs and feet but the arms and hands—"nay, and even the trunk of the body also," in certain cases of smallpox. His object, it is true, was to bring out the eruption well. He adds: "This is not altogether a new method: for Rhazes advises the patient to be kept in a kind of *balneum vaporis*, to facilitate the eruption."

Hebra appears to have had his attention drawn to the treatment of smallpox by the warm bath through observing its efficacy in the management of burns. In his practice in the Vienna General Hospital patients suffering from extensive burns have been kept in the warm bath continuously for one hundred days with good effect. "It is clear," says Stokes, "that in the case of the continued warm bath we have the conditions just mentioned completely fulfilled, and that, too, as regards the entire person of the patient."

In the paper from which I have so largely quoted, Stokes details a case in illustration of the use of the warm-bath treatment of bad smallpox. So graphic and striking as a word-picture is this clinical record that I know I shall be excused for transcribing it at length: "Not many years since," wrote Stokes (in 1872), "one of our students, a very large and robust man, was attacked with smallpox, which soon showed itself in its worst characters. The fever at first was very high, and the head-swelling and vascularity of the face intense. The *eruption was universal*, while the pustules on the face became confluent at an early period.

"Delirium set in, and the patient tore off the dressings from his face so often that we desisted from their further application. After the tenth day the condition of the patient was most appalling. The delirium continued, the circulation became every day weaker and more rapid, notwithstanding the free use of stimulants; the crusts were not only black, but on the legs here and there there was less confluence, the blackness of the worst purpura appeared—a condition held by Hebra to be always fatal. The body was one universal ulcerous sore, and the agonies of the patient from the adhesion of the surface to the bedclothes were not to be described. In addition to the usual fœtor of smallpox in the stage of decrustation, which was

present in the highest degree, there was an odor of a still more intensely pungent and offensive character, which seemed to pass through the bystander like a sword. I never before or since experienced anything similar. Stimulants alone, freely and constantly employed, seemed to preserve the patient alive; the pulse was rapid, weak, and intermittent, and for several days we despaired of his life.

"At this juncture I happened to describe the case to my colleague, Mr. Smyly, who suggested the trial of the warm bath, with the view of relieving the terrible suffering. A bath in which he could recline was speedily procured, and, pillows being adjusted in it, we lifted the sufferer in and placed him in the recumbent position. The effect was instantaneous and marvellous. The delirium ceased as if by magic; it was the delirium of pain, and the patient exclaimed: 'Thank God! thank God! I am in heaven! I am in heaven! why didn't you do this before?' The fœtor immediately and completely disappeared, so that on entering the ward no one could suppose that there was a case of smallpox in it. He was kept at least seven hours in the bath, during which time brandy was freely administered, and omitted only when he showed symptoms of its disagreeing with the brain. He was then removed to bed. The surface was clean, and in many places the sores looked healthy and white. The bath was repeated next day, after which he fell, for the first time, into a tranquil slumber. From this time his recovery was progressive, delayed only by the formation of abscesses and the great soreness of the feet.

"That this gentleman's life would have been sacrificed but for the timely use of the bath, few who have had any experience in prognosis can reasonably doubt. He was in the condition of a patient every portion of whose skin had been burned and ulcerated. The pustulation was almost universally confluent; the purulent matter highly putrescent; the hemorrhagic state developed, and the nervous system suffering—in fact, he had every symptom of the worst putrid absorption.

"This case," adds Stokes, "and its singular result, in addition to the experience of Hebra, justifies the recommendation of the use of the bath."

In a discussion on the treatment of smallpox at the Medical Society of the Royal College of Physicians of Ireland, on March 20th, 1872, Dr. Hawtrey Benson,[71] now Consulting Physician to the City of Dublin Hospital, detailed a very similar case to the foregoing. The patient was kept in a slipper-bath, at a temperature of 98° F. for five hours and a half. He was then put to bed perfectly free from delirium, and, with the help of fifteen grains of chloral (of which

sixty grains had previously had no effect), he slept uninterruptedly for eight hours. The case progressed from that time forward without the slightest check.

Hebra's apparatus for the continual bath[72] was exhibited in the London International Exhibition of 1862. The apparatus consists of a bath, six feet long by three feet broad, made of wood and lined with copper or zinc. Exactly fitting its interior is an iron frame to which are fastened transverse bands of webbing, as in an ordinary bed. About two feet from one end of this frame is attached a head support, which moves on a hinge and can be fixed at any angle by a simple piece of rack-work. The frame is covered with a blanket and is also provided with a horsehair pillow; it does not rest on fixed supports, but is suspended in the bath by cords attached to it at each end. These cords pass over two small rollers, placed one at the head, one at the foot of the apparatus and provided with handles, so that the whole bed can easily be raised or lowered within the bath. At the head of the bath, but at a higher level, is a vessel made of copper, which can be heated so that the water may be supplied at any required temperature. The supply pipe enters the bottom of the bath, the escape pipe opening into it at the water level. When the apparatus is in use water is kept flowing constantly through it, so that all impurities are rapidly washed away. To enable the face to be kept continually wet, or to be specially irrigated, additional small tubes, each provided with a rose, are connected with the copper vessel or reservoir.

Before the patient is placed in the bath it is filled with warm water, at a temperature of 90° to 100° F., according to his inclination. A wooden cover, upon which a blanket is spread, is put over the lower part of the apparatus while the patient is in the bath. If it is desired that the head also should be covered, this is easily managed by roofing in the head of the bath by means of hoops upon which blankets are placed.

Four of these baths were put up in the General Hospital of Vienna under Professor Hebra's supervision.

The treatment of such affections of the skin in smallpox as bedsores, abscesses, boils, erysipelas, and gangrene, consists largely in scrupulous cleanliness and efficient nursing. The body linen should be frequently changed. The patient should lie on a water-bed, or a woven-wire mattress, since the introduction of which into our hospital wards bedsores have become much less common than before. The intense pain which attends the formation of pustules upon the soles of the feet and the palms of the hands is due to the thickness of the epidermis, which is with difficulty raised by the exudation,

and thus causes a counter-pressure on the cutis. Our object then should be to keep these parts moist and therefore soft, and this is effected by wrapping the feet and hands in Gamgee tissue or in wet cloths covered with oiled silk or gutta-percha tissue as recommended by Hebra. If this is done, no disagreeable sensations are felt. Writing in 1764, Huxham said: "I would recommend also bathing the feet and legs in warm water, or milk and water, for a few minutes, two or three times a day before and at the eruption, and would likewise have cataplasms of *milk and bread, boiled turnips*, or the like, applied to the feet." He did this "to make a very powerful revulsion from the head and breast."

The eyelids should be poulticed to reduce œdema, or kept covered with cold compresses. For atrophic keratitis cod-liver oil, iron, wine, and good food are indicated.

Affections of the mouth, tongue, and pharynx are best treated with ice, antiseptic sprays of sulphurous acid, chlorinated soda solution, corrosive sublimate solution, or Condy's fluid well diluted, antiseptic gargles of quinine, chlorate of potassium, boric or lactic acid, resorcin (in the proportion of 10 grains to the ounce of peppermint water with glycerin) carbolic acid, and so on; linctuses of glycerin of tannin or of carbolic acid, boric acid, glycerin and lemon juice, etc.

In cases of laryngitis the internal use of ice is invaluable. Hot poultices should be slung round the neck and kept smeared with glycerin of carbolic acid or a two-and-one-half-per-cent carbolized oil. In the early stage leeches may be applied to the angle of the jaw. In like cases in scarlatina Graves recommended the application of relays of sponges wrung out of hot water to the front of the neck for fifteen or twenty minutes at a time. Above all, the steam kettle should be kept going and the patient should be placed in a croup-tent and well supported by food and stimulants. In acute œdema of the glottis, Curschmann advises that an emetic should be given, if the patient is strong enough, or local scarifications or tracheotomy may be employed.

The same measures as those advised for laryngitis may be adopted in bronchitis or other affections of the respiratory tract, in addition to dry-cupping (if the rash is not thick-set) and poulticing.

Diarrhœa is often controlled by a starchy diet and brandy or port wine, and by poulticing the abdomen, or by applying a wet compress over it. If not, solution of pernitrate of iron may be prescribed, or pills of acetate of lead and opium, or—in the case of children—aromatic chalk powders.

An excellent remedy is a small starch enema, containing ten to

twenty drops of laudanum. This stays peristaltic action. Salicylate of bismuth, salol (phenyl ether of salicylic acid), and carbonate of guaiacol, or five-minim doses of spirit of turpentine or terebene will be found useful. Salicylate of bismuth is readily swallowed in cachets even in ten-grain doses. Dr. James Little, senior physician to the Adelaide Hospital, Dublin, prescribes the drug in a pill or, should the patient be unable to swallow a pill, in a mixture. His formulæ are:

PILL.

℞ Acidi carbolici, ... gr. $\frac{1}{6}$.
Extracti opii, ... gr. $\frac{1}{6}$.
Bismuthi salicylatis, ... gr. iij.

Fiat pilula secundum artem. One such pill is to be taken after each loose stool.

MIXTURE.

℞ Bismuthi salicylatis,. . . . . gr. xxx.
Pulv. gummi acaciæ, ... gr. cxx.
Tincturæ opii, ... ♏ xviij.
Glycerini acidi carbolici, ... ʒ ss.
Tincturæ lavandulæ comp., ... ʒ iij.
Aquæ, ... ad ℥ vi.

Sig. A sixth part twice, thrice, or four times in twenty-four hours, as required.

Of late, I have found the following very useful:

℞ Bismuthi salicylatis, ... gr. lxxx.
Pulv. tragacanth. comp., ... gr. cxx.
Spt. chloroformi, ... ʒ ij.
Aquæ, ... ad ℥ viij.

Sig. Shake the bottle. An eighth part every third or fourth hour, as required.

In cases of sleeplessness and delirium, the hair should be cut close or the head shaved, ice may be applied as recommended by Stokes, unless there is much depression, and stimulants often agree. The proper alternation of day and night induces sleep, so the sick-room should not be entirely darkened in the daytime, although only the red rays should be allowed to enter. Whispering in the sick-room should be forbidden; far better to talk aloud, if it is necessary to talk at all. In private practice, the plan of having two beds and changing the patient from one to the other every twelve hours or so often brings on sleep. Should these simple nursing measures fail, and if the patient has had no sleep for thirty-six hours, recourse must be had to hypnotics.

The "three fifteens" sometimes act well, that is, fifteen grains of bromide of potassium, fifteen grains of chloral hydrate, and fifteen minims of liquid extract of opium. Pain must be relieved in small-

pox if sleep is to be secured. Foremost among anodynes and hypnotics alike stands opium, which, unfortunately, has the disadvantage of tending to lock up the secretions. Nevertheless, to an adult whose kidneys are sound and efficient, fifteen or twenty minims of Battley's sedative solution may be administered; or twenty to thirty minims of the solutions of the hydrochlorate or acetate or bimeconate of morphine, or twenty minims of "nepenthe" (a solution of pure meconate of morphine in sherry wine), or five grains of the "compound soap pill" of the British Pharmacopœia, or ten grains of the compound ipecacuanha powder ("Dover's powder"), or, better still, a pill representing that dose and consisting of one grain each of extract of opium and of ipecacuanha with two grains of extract of hyoscyamus. A hypodermic injection of morphine (gr. $\frac{1}{8}$ to $\frac{1}{4}$) may be substituted for any of the foregoing, if preferred. Graves' classical prescription of tartar emetic and opium is now seldom, if indeed ever, exhibited. Murchison proposed that digitalis should be given in combination with opium or morphine, and there is no doubt that by these combinations sleep will be induced in many instances where opium alone would fail or be contraindicated. Murchison's prescription is as follows:

℞ Liquoris opii sedativi, ... ʒ i.
Tincturæ digitalis, ... ʒ i.
Spt. ætheris nitrosi, ... ʒ ij.
Aquæ camphoræ, ... ad ℥ vi.
Sig. A sixth part at once, and afterwards half a fluidounce every second hour until the patient sleeps.

Chloral suits children much better than opium. It may be given in this form:

℞ Syrupi chloralis (B. P.), ... ʒ i.
Syrupi simplicis, ... ʒ vij.
Sig. A teaspoonful every hour until sleep sets in.

A prescription of Graves for the insomnia of the ataxic state (nervous prostration) may be quoted. It was a draught, to be taken every two hours, containing half a grain of tartrated antimony (tartar emetic), ten grains of musk, five grains of camphor, and ten drops of laudanum. After taking three such doses the (typhus) patient, whose case he was describing, fell into a quiet sleep, from which he awoke quite rational.[73]

When prescribing the bromides, it is well to order them to be freely diluted. They may be given in full doses, even up to sixty grains, at least two hours before sleep is expected.

Sulphonal, trional, tetronal, chloralamide, and paraldehyde are

unreliable hypnotics in smallpox, and therefore cannot be recommended. Phenacetin, phenazone, and acetanilide may induce sleep indirectly in smallpox by reducing temperature and relieving pain, especially headache. They should, however, be exhibited with caution and in moderate doses. These drugs are *not safe* in early childhood. A magical draught is this:

℞ Phenazoni, ... gr. xx.
Misturæ gelsemii, ... ♏ xx.
Aquæ chloroformi, ... ad ℥ ij.
Sig. One fourth part for a dose—to be repeated in two hours, if need be.

Attendants upon smallpox patients should always be on their guard against homicidal or suicidal attempts.

Curschmann recommends that chloral hydrate should be administered by the rectum, in an enema containing from one and a half to two drachms, with eight ounces each of water and of mucilage. He says that variolous affections of the pharynx and larynx may be dangerously intensified by this drug.

In cases of profound stupor, attention should be directed to the state of the bladder. Timely use of the catheter may at once relieve retention of urine and cerebral oppression and obviate a troublesome cystitis.

Thirst is best assuaged by draughts of cold water, if need be slightly acidulated or embittered with cascarilla or quassia (Murchison). According to the late Dr. Robert D. Lyons, of Dublin, camphor is often a specific against thirst. It may be given in the form of camphor julep (aqua camphoræ).

Persistent vomiting is best treated by applying a sinapism to the pit of the stomach or nape of the neck, should the state of the surface allow it; or by the administration of ice, lime water, Schacht's solution of bismuth, magnesium preparations, or effervescing draughts with dilute hydrocyanic acid. The bowels should be kept free. Tympanites or meteorism (flatulent distention of the abdomen from inflation of the intestines with gas) and hiccough must be treated with antispasmodics internally, such as thirty-minim doses of aromatic spirit of ammonia, or compound spirit of horse-radish, or spirit of cajuput, or of nutmeg, together with ten to twenty minim doses of tincture of sumbul. Other useful remedies are turpentine, peppermint with carbolic acid, creosote, or guaiacol. Enemata of turpentine, asafœtida, and rue might be administered, if there was no evidence of an intestinal variolous eruption. The best external applications are hot fomentations, poultices, turpentine epithems, and above all, ice poultices, as recommended by Dr. Peter, of Paris. Dr.

William Cayley says the ice poultice may be conveniently applied by putting small pieces of ice between two folds of flannel. Failing all these means, the long tube should be passed up the rectum as far as possible in order to give vent to some of the pent-up gas.

Lastly, while only too often it happens that all our efforts to combat *hemorrhagic smallpox* are in vain, we yet may save life by the administration of the solution or tincture of ferric chloride in full doses—thirty minims every third hour, or of gallic or tannic acid five-grain to ten-grain doses, or of pyrogallic acid in one-grain doses, or of ergot (ounce doses of the infusion or three grains of ergotin dissolved in glycerin and water, the latter dose being given hypodermically if need be), or, best of all, of turpentine and ergot. The formula for the last combination which we used at Cork Street Hospital was as follows:

℞ Extract. ergotæ liquidi, ... ʒ iij.
Olei terebinthinæ, ... ʒ iij.
Spt. ætheris nitrosi, ... ʒ ij.
Spt. rectificati, ... ℥ i.
Ovi vitellum,
Aquæ menthæ piperitæ, ... ad ℥ viij.
Sig. One eighth part every third, fourth, or sixth hour, as required.

At Cork Street Hospital, in cases of menorrhagia and metrorrhagia, cold to the vulva was of use, also slapping the buttocks with cloths dipped in ice-cold water. In several cases, hot water injected into the vagina, as recommended by Dr. Emmet of New York, and approved by Dr. Lombe Atthill, the temperature of the water being from 98° to 110° F., seemed to do good.

In these awful cases stimulants are imperatively called for, brandy, whiskey, or wine according to circumstances, and especially "egg flip" mixture and "turpentine punch." Curschmann recommends a further trial of transfusion of blood, which, he admits, has so far disappointed expectation. Inhalation of oxygen is undoubtedly of use, but the gas should not be inhaled or driven into the mouth forcibly. The mouthpiece should be held at a short distance away from, and below, the lips of the patient.

In the management of the various complications and sequelæ of smallpox, "we must" (as Murchison says, when speaking of typhus) "be guided by general principles and by the symptoms in the individual case, never forgetting that the primary disease" (and this is especially true of the terrible malady we have been considering) "has a tendency to induce great nervous prostration and depression of the heart's action, which forbid all depleting or lowering measures."

Bibliographical References.

1. Holwell: Account of the Manner of Inoculating for the Smallpox in the East Indies, London, 1767, p. 8.

2. James Moore: History of the Smallpox, London, 1802.

3. F. Porter Smith: Médical Times and Gazette, September 2, 1871.

4. Lagarde: Archives de Médecine navale, March, 1864.

5. Curschmann: "Smallpox" in von Ziemssen's Cyclopædia of the Practice of Medicine, vol. ii., 1875.

6. Marius: "Chronicon," in Bouquet's Collection des Historiens de France, Paris, 1738, vol. ii.

7. Constantinus Africanus: De Morborum Cognitione, lib. viii., cap. 8, Opp. Basel, 1536.

8. Ralph Holinshed: The Chronicles of Englande, Scotlande, and Irelande, 2 vols., folio, London, 1577.

9. Fournier: Archives de Médecine navale, September, 1874.

10. Manual of Public Health for Ireland, 1875, p. 298, Dublin: Fannin & Co. See also Buchan and Mitchell's paper in the Journal of the Scottish Meteorological Society, 1874.

11. Edward Ballard: Medical Times and Gazette, March 11, 1871.

12. Pruner: Die Krankheiten des Orients, Erlangen, 1847 (quoted by Hirsch).

13. Edgar M. Crookshank: Manual of Bacteriology, London: H. D. Lewis, 1887.

14. von Jaksch: Clinical Diagnosis. Translated by James Cagney, London: Charles Griffin & Co., 1890.

15. Hirsch: Handbook of Geographical and Historical Pathology, London: The New Sydenham Society, 1883, vol. i., p. 152.

16. A. W. Blyth: Manual of Public Health, London: Macmillan & Co., 1890.

17. F. W. Barry: Report of an Epidemic of Smallpox at Sheffield, 1887–88, London, 1889.

17a. Louis C. Parker: Hygiene and Public Health, London: H. K. Lewis, 1897.

18. William Osler: The Principles and Practice of Medicine, New York, 1896.

19. Albert H. Buck: Treatise on Hygiene, New York: William Wood & Co., 1879, vol. ii., p. 519.

20. Zuelzer: Beiträge zur Pathologie und Therapie der Variola. Berliner klinische Wochenschrift, 1872, No. 51.

21. Obermeier: Beiträge zur Kenntniss der Pocken. Virchow's Archiv, Bd. 55, S. 545.

22. Rayer: Traité des Maladies de la Peau, 1835.

23. Eimer: Die Blatternkrankheit in pathologischer und sanitätspolizeilicher Beziehung, Leipsic, 1853.

24. Th. Simon: Das Prodromal-Exanthem der Pocken. Archiv für Dermatologie und Syphilographie, II. Jahrgang, p. 347 *et seq.*

25. Osler: The Initial Rashes of Smallpox. Canada Medical and Surgical Journal, 1875.

26. The Entire Works of Dr. Thomas Sydenham. By John Swan, M.D., London: F. Newbery, 1769, p. 105.

27. Trousseau: Clinique Médicale de l'Hôtel Dieu de Paris. J. B. Baillière et Fils, 1865.

28. Wendt: Ueber das Verhalten des Gehörorgans und Nasenrachenraums bei Variola. Archiv für Heilkunde, Bd. 13, S. 118 and 414.

29. Meredith Richards: The Quarterly Medical Journal, vol. v., part i., October, 1896, p. 33.

30. Pirro Bolognini: La Pediatria, 1897, No. 3, p. 76. Abstract in La Presse Médicale, No. 37, 1897, p. 204; also in the British Journal of Dermatology, July, 1897, p. 296.

31. William Stokes: Dublin Journal of Medical Science, vol. liii., p. 9. Dublin: Fannin & Co., 1872.

32. Sternberg: A Text-book of Bacteriology, New York: William Wood & Co., 1896.

33. John MacCombie: Article "Smallpox" in a System of Medicine, edited by T. Clifford Allbutt, vol. iii. London and New York: Macmillan & Co., 1897.

34. Murchison: A Treatise on the Continued Fevers of Great Britain, third edition, 1894, p. 136.

35. J. W. Moore: Article "Typhus Fever" in a System of Medicine, edited by T. Clifford Allbutt, vol. iii. London and New York: Macmillan & Co., 1897, vol. ii.

36. Wunderlich: A Manual of Medical Thermometry. New Sydenham Society, 1871.

37. Th. Simon: Charité Annalen, xiii., Bd. v.

38. J. M. Bruce: Cyclopædia of the Diseases of Children, edited by John M. Keating. Philadelphia: J. B. Lippincott & Co., vol. ii.

39. Seppilli e Maragliano: Della Influenza del Vajuolo sulla Pazzia, Milano, 1878.

40. Combemale: Archives générales de Médecine, June, 1892.

41. Whipham and Myers: The Lancet, March 20, 1886.

42. Westphal: Ueber Nervenaffectionen nach Pocken. Berliner klinische Wochenschrift, 1872, No. 1. Also Ueber eine Rückenmarkserkrankheit bei Paraplegie nach Pocken. *Ibid.*, No. 47, quoted by Curschmann.

43. Arthur Neve: The Lancet, September 24, 1887.

44. Weigert: Anatomische Beiträge zur Lehre von den Pocken, Breslau, 1874, Theil i.

45. Ponfick: Ueber die anatomischen Veränderungen der innern Organe bei hämorroische und pustulose Variola. Berliner klinische Wochenschrift, 1872, No. 42.

46. H. Koplik: Archives of Pædiatrics, December, 1896.

47. E. M. Crookshank: History and Pathology of Vaccination, London: H. K. Lewis, 1889.

48. C. E. Shelly: Article "Disinfection," in Fowler's Dictionary of Practical Medicine, London: J. and A. Churchill, 1890.

49. Manual of Public Health for Ireland, Dublin: Fannin & Co., 1875, pp. 172 and 173. Also Special Report on the Smallpox Epidemic, 1871–73, as Observed in Cork Street Fever Hospital, Dublin. By T. W. Grimshaw, M.D. Being an Appendix to the Medical Report of that Hospital for the year ending March 31, 1873. Dublin: John Falconer, 1875.

50. S. Coupland: The Lancet, February 20, 1897; The Hospital, August 14, 1897.

51. Phineas S. Abraham: On the Alleged Connection of Vaccination with Leprosy. Transactions of the Seventh International Congress of Hygiene and Demography, London, 1891, vol. i., p. 384.

52. Journal of the Leprosy Investigation Committee, No. 4, December, 1891, p. 32.

53. C. Black: The Lancet, June 29, 1867.

54. J. H. Waters: The Action of Light in Smallpox. The Lancet, February 4, 1871.

55. W. H. Barlow: The Lancet, July 1, 1871.

56. Gallavardin: Traitement de la variole par l'obscurité solaire. Lyon Médical, June 12, 1892.

57. Niels R. Finsen: Om Lysets Indvirkninger paa Huden. Hospitalstidende, July 5, 1893.

58. Unna: Ueber das Pigment der menschlichen Haut. Monatsheft für praktische Dermatologie, 1885, p. 285.

59. Widmark: Ueber den Einfluss des Lichtes auf die Haut. Hygiea, Festband, No. 3.

60. Hammer: Ueber den Einfluss des Lichtes auf die Haut, Stuttgart, 1891.

61. Charcot: Comptes rendus de la Société de Biologie, 1859.

62. Lindholm: Hospitalstidende, 1893, p. 919.

63. Juhel-Renoy: Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris, December 14, 1893.

64. C. Feilberg: Behandling af Kopper med Udelukkelse af Dagslysets kemiske Straaler. Hospitalstidende, July 4, 1894.

65. Arthur Wynne Foot: The Dublin Journal of Medical Science, vol. liii., pp. 242 *et seq.*

66. E. Pepper: American Journal of the Medical Sciences, March, 1893.

67. William Stokes: Dublin Journal of Medical Science, vol. liii., 1872, p. 9.

68. Lewentauer: Bulletin Général de Thérapeutique, No. 32, 1869.

69. Bertrand: Gazette des Hôpitaux, July 15 and 17, 1890.

70. Talamon: La Médecine Moderne, April 17, 1890.

71. Hawtrey Benson: Dublin Journal of Medical Science, vol. liii., p. 325, 1872.

72. Hebra: Wiener allgemeine medizinische Zeitung, No. 43, 1861; and Diseases of the Skin, translated for the New Sydenham Society by Hilton Fagge, 1866.

73. Robert James Graves: Clinical Lectures on the Practice of Medicine. Edited by John Moore Neligan, Dublin: Fannin & Co., 1864, p. 177.

The literature of smallpox to 1885 will be found in the thirty-eighth volume of the "Nouveau Dictionnaire de Médecine et de Chirurgie pratiques" under the headings "Vaccine" and "Variole." Reference may also be made to articles on "Variole" and "Vaccine" in "Les Bactéries" by Cornil et Babes, to the *Centralblatt für Bakteriologie und Parasitenkunde*, and to p. 34 of Flügge's "Microorganisms," published by the New Sydenham Society, London, in 1890. Lastly, in the *Hygiea* (Stockholm) for June, 1896, p. 607, E. W. Dahlgren gives a very complete list of Swedish contributions to the literature of smallpox, inoculation, and vaccination from the beginning of the sixteenth century (1505) to the present day.

VACCINA.

BY

P. BROUARDEL,

PARIS.

VACCINA.

During the eighteenth century epidemics of smallpox followed each other in rapid succession throughout the entire world. The documents which we possess concerning the ravages of variola in France, England, and Germany give nearly the same figures as regards the mortality caused by this disease, an epidemic of smallpox destroying about two thousand persons per million inhabitants, that is to say, two per thousand. This estimate is confirmed by what we see at the present day when variola attacks a people not protected by vaccination. In 1887 and 1888 an epidemic broke out in Douarnenez, a small city of about ten thousand inhabitants in Finistère, where vaccination had been singularly neglected, and nineteen hundred and thirty-one persons, nearly one-tenth of the entire population, perished.

In the presence of such disastrous results a procedure which rendered those who had submitted to it immune to future attacks, namely, variolic inoculation, had been received with enthusiasm. We need not stop here to discuss the advantages and dangers of this method. Those who were opposed to inoculation claimed that it was not always benign in its results; that a certain number of those who submitted to it, two or three per cent., died; and that it furthermore created a group of persons who constituted a dangerous centre of infection in the community. Furthermore it was extemely difficult to generalize this operation, and it was practically never employed outside of the small circle of those who constituted at that time the people of quality, the devoted followers of fashion. Such was the situation when Jenner appeared.

Discovery of Vaccination.

The discovery of vaccination has often been ascribed to chance; the following is the part which chance played in it: While still a student at Sudbury, Jenner saw a young woman who declared that she was safe from contracting smallpox since she had already had cowpox. This assertion was retained in Jenner's memory and served as the point of departure for his subsequent researches, and herein

precisely is the merit due him. Others before him had heard similar statements from dairymaids, and other physicians had had under their eyes similar facts. Some time before this, during the reign of Charles II., the Duchess of Cleveland, who held a position in the King's service the chief function of which was in close dependence upon her beauty, replied to the courtiers who were joking with her on the possible loss of her occupation through the disfigurement of smallpox, that she had nothing to fear, for she had had the cowpox. Some years before the appearance of Jenner's[1] memoir on the cure of variola by the cowpox, a woman named Catherine Wilkins, who had had cowpox, was in London and placed herself under the care of Archer, who tried in vain to inoculate her with smallpox. The history of the farmer Jesty is still more instructive. This man, who had seen the results of inoculations with cowpox and who appreciated their full value, submitted to the operation with his entire family. Sure of the protection afforded by the cowpox, he came to London, to the inoculation hospital, and defied the physicians to give him or any of his family the smallpox. The physicians of the smallpox hospital, who had thus a grand discovery thrust into their hands, failed to see in this circumstance anything extraordinary. Jenner's distinction over his colleagues is that he did understand the significance of this fact. He was a pupil of the great John Hunter, the man who maintained a regular menagerie for his laboratory experiments, to which he was devoted, his patients being regarded solely as a means of supplying that "damned guinea" needful in the maintenance of his museum. Jenner himself had made a large number of experiments; he had carried on with his master a correspondence in which we find with astonishment that they discussed questions which to-day arouse the liveliest controversy, as, for example, the electrical apparatus of the torpedo, the phenomenon of hibernation, the temperature of animals and vegetables, muscular movements, etc.

Jenner, after leaving London, returned to his native place to establish himself in practice, and there carried on with great zeal inoculation for smallpox. He soon remarked that certain persons were refractory to his variolous inoculations, and, guided by the recollections of his student observations, he soon noticed that this immunity was possessed by persons who had to do with the care and milking of cows. The first serious observations of Jenner were apparently made in 1775. He saw that an eruption occurred on the hands of the cowherds and dairymaids, especially when there were chaps and cracks in the skin, and that this eruption was characterized by the appearance of vesicles similar to those on the udders of the cows. As early as 1787 he appears to have believed that cowpox originated

in the contagion of grease in horses. In his memoir on Jenner, Lorain describes most clearly the result of all these observations. "We know," he said, "the date of the first vaccination as we do that of a great battle; it was May 14th, 1796. On that day Jenner took vaccine from the hand of a young dairymaid, Sarah Nelwes by name, who had been infected by her master's cow, and inserted it through two superficial incisions in the arm of James Phipps, a large boy of eight years. This succeeded perfectly, and the vaccine from this child served to vaccinate several other children. James Phipps, inoculated two months later with variola, was refractory. The proof was made." But Jenner, anxious not to announce as a fact what might be refuted, repeated this experiment frequently and made others, and did not finally publish his discovery until he was absolutely certain that there was no possible error in his deductions.

In all these experiments we find nothing to suggest the identity of human smallpox and the protective disease in animals, with the belief in which J. Guérin credits Jenner. Theoretically, indeed, Jenner thought that all animals are subject to a disease which is a form of variola peculiar to each species. For example, he regarded grease as an equine smallpox, but he did not conclude from that that all these forms of variola constitute but one morbid entity, differing among themselves only as a consequence of the difference in the soil in which the disease develops. He held that our domestic animals, such as horses, cows, sheep, swine, dogs, and some others are subject to a form of eruptive disease. Possibly also fowls are to be included in this list, in which case we should find a justification for the name of chickenpox applied to an exanthem affecting man. In Bengal chickens suffer from an eruption resembling smallpox, which sometimes prevails epidemically and kills great numbers. In order to arrest the progress of this disease among fowls a trial has been made of inoculation. The natives have but one name, *gootry*, for smallpox and for this disease in fowls. Jenner believed that cowpox is not a disease peculiar to cows, but that it originates in the horse, is carried by infection to the cow, and thence to man.

The Relations of Cowpox, Horsepox, and Vaccina in Man.

The experiments of Jenner and the doctrinal views based upon them have served as points of departure for all subsequent works. We have just said that Jenner was convinced that cowpox originated in the horse and was carried from horses to cows by the stable boys and dairymaids. He called the disease of the horse, which he

regarded as the source of vaccina, by the term grease, and subsequently sore-heels. The French translators of Jenner committed the error of giving as the equivalent of this indefinite term the word *javart*, which has a precise meaning very different from that attached to the term sore-heels by Jenner. This error had a great influence on subsequent experiments in France.

The arguments which Jenner advanced in support of his opinion were the following: When sore-heels prevails among horses the cows in the neighborhood have cowpox; and blacksmiths and stable boys, who are brought into such constant contact with these animals, are most commonly refractory to inoculation with vaccina or variola. Jenner tried to inoculate heifers with the virus of sore-heels, but his attempts were unsuccessful. He nevertheless remained no less convinced of the correctness of his theory, and by a simple anecdote he demonstrated the mode in which contagion occurs. Lord Asaph, he said, had a horse affected with grease; this animal was shut up in an isolated stall at some distance from the stables, but in spite of this precaution all the cows on the place were soon attacked with cowpox. Such an interesting fact aroused general attention; an investigation was undertaken and resulted in the discovery that one of the grooms who had the care of the sick horse was in the habit of helping his sweetheart, a dairymaid, to milk the cows, and he had been the carrier of the virus.

Since Jenner's time hundreds have made experimental inoculations of the grease. In some of these experiments cowpox followed the inoculation, in others it did not. Some observers obtained varying results under apparently exactly similar conditions. Thus Coleman, a veterinary surgeon, was led by his early experiences to reject Jenner's theory, but was led to reverse his views by the results of a second series of experiments.

The question was in this undecided state in France when there happened what has been called the Toulouse occurrence, an account of which we shall borrow from the report made by Bousquet to the Académie de Médecine. There suddenly occurred in the spring of 1860 at Rieumes, near Toulouse, an epizootic among the horses; in less than three weeks more than three hundred animals had been attacked. At this time, it may be noted, smallpox was prevailing in the neighborhood. A veterinary surgeon at Rieumes, M. Sarraus, has described this epizootic. It began with a mild fever, and following this local symptoms occurred, chief among which were a swelling of the leg and lameness; this swelling seemed to be made up of a mass of little pustules. This was the first stage, which lasted from three to five days, and was followed by a purulent discharge from

about the hoof. This lasted eight or ten days. Finally the pustules dried up, leaving well-marked cicatrices. There were also single pustules disseminated over the body, at the vulva, on the lips, and in the nostrils. There were no cases of cowpox at this time on any of the farms in the vicinity. According to Sarraus, of these hundred or more animals only three mares and two stallions had acquired the disease from without, the rest having become affected through contagion. The contagion took place at the stud of Sarraus, where the animals were tied by shackles made of rope.

This is the description given of the epidemic; the following is that of the experimental and truly demonstrative part of the event. A mare belonging to M. Corail was brought to the veterinary school at Toulouse. The eruption which it presented had all the characteristics of that just described. On April 25th, M. Lafosse, clinical professor at the veterinary school, inoculated a young cow with matter taken from the pustules of this mare, the insertion being made in an incision on each of the cow's teats. On May 3d, the teats were covered with vesicles which were diagnosed by all the profesors of the school as the exanthem of cowpox. Other cows were inoculated, and children were also inoculated with this cowpox. Humanized vaccine virus was inserted into one arm and this cowpox virus in the other; the results showed that there was no difference whatever between the two forms of virus. Now what was this epidemic? According to the opinion of the professors at the veterinary school of Toulouse and that of Leblanc, it was neither grease nor eczema of the feet, and whether or not it was a new vaccinogenous disease was not determined.

Bouley[2] occupied himself with this question and, after having reviewed the opinions of Jenner and others, resolved to inoculate heifers with every eruptive disease of the horse. By chance the first disease of the horse which he had to study gave rise to cowpox by inoculation. This malady was diagnosed by him as aphthous stomatitis, and he believed that this experiment added to that of Toulouse proved that the horse is vaccinogenous, and that we must add a new malady to those already reputed to be generators of cowpox, such as grease or sore-heels of Jenner, javart of Sacco, the furunculous disease of Hertwig, and the pustulous malady of Lafosse. Bouley invited his colleagues of the Academy to come to Alfort to study this disease, and soon the question entered into a new phase.

Depaul and Bouley seem to have simultaneously recognized the true character of this new malady. It is not an aphthous stomatitis, as Bouley at first supposed, but is a general exanthematous disease having a pustulous eruption covering nearly the entire body, but

most distinctly localized about the hoofs and in the mouth; in a word, it is an eruptive disease which should be ranked along with smallpox in man, and which is, indeed, according to Depaul, identical with it. Bouley gave it the name of horsepox, and there is now no longer any question of a variety of different diseases all capable of producing cowpox; there is but one vaccinogenous equine disease, but this disease has numerous localizations, and each of them has in succession been regarded as alone constituting the disease. This disease is directly inoculable in man, as was once shown accidentally in the case of one of the students at Alfort, and once intentionally in the case of a child vaccinated by Bouley.

This question is therefore settled, namely, that the horse is subject to a vaccinogenous malady which is horsepox. This disease when transported to the cow gives rise to cowpox, and when transported to man produces vaccina.

Are there any other vaccinogenous diseases? Formerly foot-rot and the aphthous disease were regarded as such. Hurtrel d'Arboval vaccinated 1,523 sheep, and in 1,340 the operation was successful. Of these 429 were exposed to foot-rot and 308 were attacked. Thus vaccina does not protect sheep from foot-rot. Sacco claims to have produced foot-rot in man, and to have obtained successful vaccination from these cases; but although this experiment has been very frequently repeated it has never since given positive results. It may be assumed, therefore, that foot-rot has wrongly been included among the sources of vaccina. We shall see also that the members of the Lyons committee have proved incidentally that aphthous fever cannot be the same disease as cowpox. Indeed animals that only a short time previously were affected with aphthous fever have been successfully vaccinated, and have had a very typical vaccinal eruption, thus affording sufficient proof of the independence of these two affections. We may say, therefore, that as yet we know of but one disease in animals which can give rise by inoculation to cowpox, and that disease is horsepox.

This spontaneous horsepox differs from inoculated horsepox, as all virulent diseases when occurring spontaneously differ from the same diseases when produced by inoculation. We may ask what is the cause of this dissimilarity and what we are to understand strictly by the word "spontaneous." As this question in general pathology has been studied especially in relation to horsepox, we may as well discuss it here.

Can horsepox arise spontaneously, or must we maintain that there is always contagion, the transportation of some germ which will sow the disease where it happens to alight? Those who incline to the

doctrine of spontaneous generation of virus invoke a rather strong argument in support of their theory. When a horse or other animal is inoculated with horsepox the eruption is produced at the point where the inoculation has been made, and it does not become generalized except in some rare instances, the explanation of which will be given later. In natural, spontaneous horsepox, which has occurred without inoculation, there is not a local eruption, but rather a general, or, better, a generalized eruption, that is to say, one occurring on the mouth, nose, hoofs, etc. This is, they say, a difference which proves that we have to do with two diseases with distinct evolutions; and we must admit that one arises spontaneously, under the influence of individual, as yet unknown conditions, and that the other is the simple result of inoculation.

Chauveau has, however, taken away this argument from the partisans of the spontaneous origin of the virus. In the case of a horse he exposed a lymphatic and injected some vaccine virus into the vessel. The result of this was an eruption precisely similar to that of spontaneous horsepox. This eruption, which I cannot stop to describe here, occupies exactly the same seat as that of the spontaneous disease; it is generalized, and produces no local lesion of vaccinal nature at the point of inoculation. Precisely the same result was obtained when Chauveau injected vaccine into the jugular vein or into the subcutaneous cellular tissue, or even when he caused the animal to swallow food impregnated with vaccine virus. From this he concludes that the penetration into the economy of vaccine virus by any channel other than the skin will give rise to an eruption identical with that of spontaneous horsepox. We can therefore invoke no special form of the eruption in proof of the theory of the spontaneous origin of the virus.

How does it happen that, by cutaneous inoculation, in the great majority of cases we obtain only a local eruption? We may conceive that the skin being the actual seat of election of the manifestations of the disease, there occurs from the beginning at the injured point a process capable of exhausting the sum of all the possible manifestations of the affection, but this is pure hypothesis. On the other hand we may easily explain the rare cases in which a general eruption has been seen to follow cutaneous inoculation with the virus, by assuming that there has been an accidental insertion of some of the vaccine into a lymphatic vessel.

We know then to-day that horsepox is a source of vaccina, and that the contagion of horsepox in horses may occasion that form of the affection which has been described under the name of spontaneous horsepox.

The Non-Identity of Variola and Vaccina.

During this discussion another question has arisen. For a long time authors believed that cowpox, grease, and variola had but one common origin and that the virus was the same in each disease. Thiélé and Ceely, not being able to procure vaccine matter, inoculated a cow with virus taken from a man suffering from smallpox and transmitted to successive generations the product of this inoculation. Was the disease so produced vaccina, or did these experimenters simply return to the old practice of variolous inoculation?

Depaul,[3] who had had the opportunity to study at Alfort the vaccinogenous affection discovered by Bouley, regarded it as smallpox in the horse, and did not hesitate to affirm before the Académie de Médecine that (1) there is no vaccine virus; (2) the alleged vaccine virus which is regarded as antagonistic to the variolous virus is nothing else than variolous virus itself; (3) the bovine and equine species are subject to an eruptive disease which is identical, as regards its nature, with smallpox in man. According to Depaul, therefore, horsepox, cowpox, vaccina, and variola are identical affections, all having smallpox as their common source. He believes that it is one and the same disease which changes its form, develops completely or incompletely, according as it affects one or the other animal. The virus of one form of the disease may transform itself into that of another when transferred to the soil proper to this last.

Some of the academicians were as much astonished by this proposition as horticulturists would be surprised were some one to tell them that seeds taken from the same fruit would produce different fruits if planted in different soils. Bouley in vain called for inoculation experiments which might demonstrate the actual facts. Depaul did not give the proof, and the discussion was closed. The academicians ranged themselves into two nearly equal camps, and between the two was J. Guérin with his theory of hybridization, the cowpox humanizing itself in man and equinizing itself in the horse.

This question is to-day settled, and, like all those which we have thus far studied, it has been settled by experiment. Chauveau, of Lyons, with some of his colleagues of the Lyons Medical Society, Viennois, Meynet, Delore, Lortet, and others, instituted some experiments which appear to us to leave absolutely no doubt as to the non-identity of variola and vaccina. The members of the Lyons committee commenced their researches with the preconceived idea, as Chauveau admits, that Depaul's opinion was the correct one. The existing conditions were excellent for the comparative study of vac-

cina and variola in the bovine species. Two large dairies were placed at the disposal of the committee, one by Lœuillet, director of the school of Saulsaie, where there were one hundred and sixty head of cattle, and the other by Cabet, in the park of the Tête d'Or, in which there were about one hundred animals. In the two establishments most of the animals were native and all the conditions of health from the time of their birth were known, and the experimenters could be sure of having to do only with animals which had not previously had cowpox, which would naturally have vitiated the results of the experiments. This disease had never occurred at Saulsaie, while at Tête d'Or there had a short time previously been an epidemic of aphthous fever, so that the opportunity presented itself incidentally of determining the non-vaccinal nature of this disease, to which we have referred above.

Some animal vaccine, cowpox, for the experiments, was furnished by Palasciano, of Naples, and Lanoix, of Paris. In the first series, thirty beasts, selected without distinction of sex or age, were inoculated, and in all of them without exception a beautiful vaccine eruption was obtained. In all the cases the eruption remained strictly localized. In a second series, about twenty animals were inoculated with humanized vaccine, vaccine recently engrafted on man, or old Jennerian vaccine. The success was almost as complete as in the first series, failure to take occurring in only one case in which the vaccine was collected a little too late. The Lyonnaise Committee succeeded therefore as well as did Bousquet in the attempt to inoculate animals of the bovine race with humanized vaccine; it was even more successful, for results were obtained in the case of old animals as well as in that of calves, and with old Jennerian vaccine as well as with vaccine recently implanted in the human species. Furthermore, the cowpox so produced was as typical (as shown by the plates inserted in the committee's report) as true cowpox; and this cowpox derived from humanized vaccine could be transmitted to human beings and cows for several generations without being changed. In the absence of any true cowpox vaccine, Chauveau, Viennois, Meynet, and others often made use of this artificial cowpox in the vaccination of children, and the eruption produced thereby was as typical as that following inoculation of genuine cowpox. These two series of experiments gave perfectly distinct and unmistakable results, and prove clearly the identity of cowpox and of vaccina cultivated in the human species.

Let us see now whether inoculations with true smallpox virus gave the same results. Seventeen young animals, heifers and bullocks, companions of the preceding, were inoculated with the virus of small-

pox. The inoculations were made with the greatest care, but none of the animals acquired cowpox. The inoculations were not absolutely without effect, for in every case there was a formation of very small reddish papules which disappeared rapidly by a sort of absorption without leaving any scab. We may conclude from this that vaccine virus and that of smallpox do not give identical results. But what was the papular eruption determined by the inoculation of variola? Was there anything specific about it, or was it simply the result of inflammation caused by the puncture? Fifteen of these seventeen animals were also vaccinated, ten of them with the virus of genuine cowpox, five with humanized virus. Of these fifteen animals only one showed a typical cowpox eruption, on three there were transitory and imperfect vaccinal pustules, and in the remaining eleven the vaccination did not take at all. Here was a new fact of capital importance, for it proved that the papules produced in the bovine species by variolous inoculation constituted a specific eruption, and that this eruption was related to cowpox just as vaccina and variola are related in man; that is to say, variola protects the bovine race from cowpox just as vaccina protects the human race from smallpox.

Let us now see what this variolous eruption in the cow is. Is it merely a rudimentary cowpox which would need for its development only to be cultivated for a certain time in animals of the bovine species? The Lyonnaise experimenters excised the variolous pustules obtained in these animals, and scraped from them a little serous fluid. With the fluid so obtained several animals were inoculated, but the results were less marked than in the primary inoculations or were absent altogether. The only conclusion which we can form from this is that the result of smallpox inoculation in these animals is something entirely different from cowpox.

Is it purely and simply smallpox? In order to determine this a non-vaccinated child was inoculated with the serous fluid obtained from these variolous papules and the result was a generalized confluent smallpox. A second child was inoculated with virus taken from the primary pustule in the first child, and it had a discrete but perfectly characteristic smallpox. The eruption in these cases was not that of a generalized cowpox, but it was the papular eruption of bovine variola. We may conclude, therefore, that smallpox may be transmitted by inoculation to the cow, but it is not transformed into vaccina in the organism of this animal; it remains variola and reacquires the characteristics of variola when implanted again in the human species.

Experimental inoculation of vaccina and variola in the horse gave exactly similar results. It is needless to describe these experiments

in detail, for they were conducted under the same conditions and with the same precautions, and gave precisely the same results.

We may admit with the committee of Lyons that human smallpox can be transmitted to animals of the bovine and equine races with the same certitude as vaccina, but the effects produced by the inoculation of the two forms of virus differ totally. In cows variola inoculations produce simply an eruption of papules so minute that they might easily be overlooked if one were not on the watch for them; vaccina inoculations, on the other hand, give rise to a typical vaccinal eruption with its large and very characteristic vesicles. In the horse, smallpox inoculations also produce a papular eruption unaccompanied by secretion or scabbing. Although this eruption is much larger than that of variola in the cow, it can nevertheless not be confounded with horsepox, the lesions of which are so remarkable by reason of the abundance of secretion and the thickness of the crusts.

Either vaccine or variola, when inoculated separately, generally confers immunity against a subsequent visitation of either disease.

When cultivated methodically in these animals, that is to say, transmitted from heifer to heifer or horse to horse, the lesions of variola never approach those of vaccina. The smallpox remains constantly what it was originally or else it tends to die out entirely, and if it is transplanted again to man it produces variola. Taken again from man and inoculated into the cow or the horse, it does not, any more than before, cause cowpox or horsepox.

Thus we see that, despite the evident relation between variola and vaccina, in both the human and the bovine or equine races, these two affections are nevertheless perfectly distinct and independent one of the other in their essence and cannot be transformed one into the other. Consequently, in vaccinating according to the method of Thiélé or Ceely, we practise the ancient smallpox inoculation, possibly rendered more certainly and constantly benign by the precaution which is taken of inoculating with the lymph of the primary lesion only, but which has most certainly retained all its dangers to the community as regards contagion.

That which seems to me to be the new and essential portion of this Lyons report, and which constitutes its superiority over accounts of previous experiments, is that the members of the committee were not content with inoculating from man to the cow or from the cow to man, but the circle was completed by studying the effects of the culture of the virus of these two diseases, carried from man to the cow and then back again from the cow to man. The chain was thus completely re-

established, and we see that after the conclusion of these experiments each virus had preserved its own specificity, its individuality, whatever may have been the soil in which it was cultivated.

The question would seem to have been settled, but it has been again agitated in recent years. Those who have maintained the unity of variola and vaccina have claimed that, contrary to the conclusions of Chauveau, the inoculation of smallpox virus into the bovidæ occasions sometimes an eruption of ephemeral papules and sometimes one of pustules which they say constitute the source of variolovaccina. These last-named lesions do not appear, they claim, in the fourth generation, as Chauveau said, but are reproduced indefinitely. To obtain these results it would be necessary to collect the variolous lymph at the moment of eruption (Voigt, 1881; Fischer, 1886), to inoculate not only the fluid portion but also a part of the substance of the pustule, and to make the inoculations not by a simple puncture but by incision and scarifications. Eternod and Haccius (Geneva, 1890) are said to have obtained the same results by denuding the derma and spreading on this surface a pulp made from the entire pustule. By practising these inoculations on young calves or on cows that had recently calved, variolovaccinal pustules were obtained which became more and more distinct after several generations. These experiments were repeated by Chauveau, who obtained variolous pustules by inoculations of the variolovaccine of Eternod and Haccius into two cows.

Pourquier and Ducamp remark that contamination of the punctures with vaccine was not impossible, for "asepsis was practised before and during the operation, but none after it." Voigt himself stated in a letter to Dupuy (Surmont[4]) that he had obtained variolovaccina in only one case out of ten attempts. Juhel-Renoy[5] and Dupuy,[6] repeating the experiments of the unicists, were unable to obtain the same results, and they declare themselves as convinced of the duality of the two forms of virus. I may add that personally, having witnessed a great number of these experiments, I am persuaded of the duality of the affections.

The Active Elements of Vaccine Virus.

The virulent fluid furnished by the vaccine vesicle is a complex product, analogous in its composition to all the non-specific pathological serous fluids. Chemical and microscopical examinations reveal the presence of no special elements to which we can attribute the peculiar activity of the vaccine. This activity necessarily resides in the elements which go to make up the vaccinal fluid, but the ques-

tion to be decided is whether it resides in all these elements or whether it is confined to certain among them.

Chauveau tried to solve this question by examining separately all the different parts of the vaccine. In order to study the special activity of vaccine lymph it was necessary to obtain the fluid entirely deprived of its solid constituents, and this was a very difficult matter. By filtration and decantation it was possible to remove the leucocytes from the plasma, but this fluid still retained granules, the most numerous of the solid elements. Chauveau found that the fluid remained just as virulent when it was deprived by decantation of its leucocytes. He mixed the vaccine matter with ten times its weight of water in order to diminish its density and viscosity, without altering sensibly its specific activity. This diluted fluid was allowed to rest in a test-tube for twenty-four hours, at the end of which time it was found that nearly, if not quite all of its leucocytes had been deposited at the bottom of the vessel. The superficial layer was then aspirated off with a pipette, and was examined under the microscope to make certain that it contained no leucocytes. If it was found to be entirely free from these elements it was employed for cutaneous inoculation, and it was found to give rise to the formation of vaccinal vesicles. Thus it was shown that the leucocytes do not contain the specific principle of the vaccine.

Chauveau was also able to deprive the fluid of all its granular elements by means of diffusion. Some vaccinal serum was carried down to the bottom of a very small test-tube, care being taken that none of it touched the sides of the vessel above the level which the fluid reached when resting in the tube. Then a layer of distilled water was added, every precaution being taken not to produce any current capable of determining mechanically a mixture of the two fluids. There was then in the test-tube a liquid column formed of two layers of different density and composition: an upper one consisting of pure water, and a lower one of vaccine matter containing with the solid elements of the latter all the dissolved substances which enter into the composition of the vaccinal fluid. The test-tube was left in a room with even temperature, and the fluid was protected from evaporation and from anything that could in any way disturb it. The leucocytes and granular particles remained in the lower layer of fluid, but the dissolved albuminous and saline matters passed by diffusion into the aqueous layer, some rapidly and others more slowly according to their respective diffusibility. After the lapse of sufficient time to allow the thorough diffusion of the soluble constituents of the vaccine through the upper layer, the fluid was drawn up little by little by aspiration into capillary tubes, so that the first tubes

contained all the soluble elements of the vaccine virus, and the second set contained these substances plus the granules and suspended corpuscles, that is to say the entire vaccine in more or less diluted form.

Chauveau made a series of comparative experiments by inoculating childen, heifers, and young horses with these two fluids. The inoculations made with the lower layer, that is to say, with the entire vaccine, were as successful as those made with pure vaccine virus; the others, made with the dilute plasma containing no corpuscular elements, failed in every instance. A chemical examination of this upper layer showed that it contained a great quantity of albumin, so that neither the absence of this fundamental substance nor the great dilution could be invoked to account for the inactivity of this fluid. The conclusion derived from these experiments is, therefore, that the fluid portion of the vaccine is not virulent and that the activity resides in the figured elements.

Some objections might be urged against the conclusiveness of these experiments. Thus it might be assumed that the virulent principle resided in the plasma, but that it was not so readily diffusible as were the albumin and the salts. Against this objection Chauveau urged that, if this hypothesis were true, an extremely diluted vaccine, being homogeneous, should always give the same results, the inoculations being always successful or always unsuccessful. On the other hand, if the virulent principle resides in the granulations, upon diluting the vaccine with a large mount of water, we ought to obtain now positive and now negative results, according as the lancet took up by chance a greater or a smaller number of the specific granulations. Now, inoculations made with vaccine diluted with twelve to fifteen times its weight of water are almost always successful; those with vaccine diluted with fifty times its weight of water are most frequently unsuccessful, although Chauveau obtained one success in every ten trials with vaccine diluted with one hundred and fifty times its weight of water. With dilutions between the two extremes of twelve and fifty the vaccination sometimes takes and sometimes fails, the failures being more numerous as the dilutions are weaker.

Still another experiment in support of this view was made by Chauveau. We have just seen that very dilute vaccine introduced on the point of a lancet produces positive results only exceptionally. If the reason for this is that the virulent granulations are so widely separated in the dilute vaccine that they are only occasionally taken up on the lancet, then inoculation with a large quantity of the diluted vaccine ought to succeed in every instance; and this is actually what happens. As a result of the experiments which we have just detailed

Chauveau concluded that the active principle of vaccine resides in the figured elements and not in the plasma.

This was the state of the question in 1867, and later researches have confirmed the results of these beautiful experiments. Unfortunately, however, we have not yet arrived at a certainty as to the nature of these virulent elements. Keber in 1868 agreed with Chauveau that the fine granulations contained in the vaccine lymph were the active elements. Straus, Chambon, and Saint-Yves Ménard[7] made experiments with the fluid obtained by passing vaccine under pressure through a plaster filter and found that it was non-virulent, thus confirming the previous experiments of Chauveau.

Pasteur, Koch, Straus, and others have endeavored without success to isolate the microbe of vaccine. Quist, of Helsingfors, Voigt, and Buttersack claimed to have discovered the specific agent, but many other experimenters have failed to confirm their supposed discovery, stating that the microbes found were those of secondary infection and were not the pathogenic organisms of vaccina.

The accidental microbes found in vaccine lymph are, indeed, very numerous. Among them are the bacillus subtilis (Vaillard and Antony), the bacterium termo, the proteus vulgaris, a saccharomycete (Pfeiffer), and a micrococcus (Vaillard and Antony). The latter was found fifteen times out of twenty examinations, and was sometimes the only one found in fresh lymph from the heifer. In addition to these we may mention also, and especially because of the dangers arising from their presence and the consequent necessity of precautions in the preparation of vaccine lymph, the microbes of suppuration, the staphylococcus pyogenes aureus, and the staphylococcus albus (Straus, Chambon, and Saint-Yves Ménard).

Although it is still doubtful whether the active agent of vaccine has been discovered, we nevertheless know some of its characteristics. For example, it resists the action of cold very well, but it loses its virulent properties at a temperature of about 50° C. (122° F.).

The Normal Vaccinal Eruption.

The eruption such as it was described by Jenner has not varied at all, whatever have been the modifications in the methods of inoculation or in the source of the vaccine.

The type which we shall choose for our description is that furnished by a child who has not previously been vaccinated and who has been subjected to no influences which might alter its condition of receptivity. The eruption may be divided as regards its course into five periods:

1. *Period of Incubation.*—This stage lasts three days. The points where insertion of the virus was made are usually the seat of a slight redness for a few hours; this disappears ordinarily to reappear again toward the end of the third day. Sometimes the skin remains a little swollen at the point of inoculation, the lesions resembling an insect bite. According to Hervieux, this period lasts but two days and not three.

2. *Period of Eruption.*—During this stage, occupying the fourth and fifth days, there is seen a little reddish elevation constituting a true papule. By the fifth day the epidermis becomes raised, forming a whitish or bluish circle, in the centre of which there is a small rounded depression called the umbilication.

3. *Period of Secretion.*—This occupies the sixth, seventh, eighth, and ninth days. Towards the end of the fifth or in the sixth day the papule enlarges and there is formed a flattened umbilicated vesicle, surrounded by a bluish, sometimes silvery lymphogenous zone. The vesicle forms a very distinct projection above the surrounding surface of the skin. Towards the seventh day the derma can be felt beneath as a nearly always indurated plaque. On the eighth and ninth days the vaccinal sore attains its height—has matured. The contents of the vesicle then become turbid and the lesion resembles a pustule of rounded shape, projecting at the sides, and flattened at its centre. Its diameter varies from 6 to 12 mm. (¼ to ½ in.) The inflammatory areola increases in size, and the subjacent derma is distinctly indurated. If the wall of the vesicle is punctured, a little sticky serous fluid escapes drop by drop during eight or ten minutes, but the lesion does not flatten down. This liquid is the vaccine lymph which, collected at this time, is to be employed for subsequent vaccinations. By the ninth day this lymph is no longer transparent, but becomes opalescent, this being the so-called stage of suppuration or purulent transformation of the vaccinal sore (Layet[8]). The skin is now less swollen, the umbilication disappears, the inflammatory zone becomes less pronounced, but the lymphatic ganglia in the neighborhood sometimes become swollen and painful at this time.

4. *Period of Desiccation.*—This stage occupies the tenth, eleventh, twelfth, thirteenth, fourteenth, and fifteenth days. The inflammatory phenomena subside, the periphery of the sore is no longer projecting, the epidermis covering the pustule becomes wrinkled, dry, brown, then blackish, and about the thirteenth day the scab begins to form, beginning in the centre and gradually covering the entire pustule.

5. *Period of Cicatrization.*—This stage occupies from the eighteenth to the twenty-second day. The scab dries and contracts more

and more, and falls off on the twenty-third day (Chambon, Saint-Yves Ménard), the twenty-fifth or twenty-sixth day (Layet), or in the third or fourth week (d'Espine.) There is left a scar, goffered in appearance, at first reddish and later of an absolutely characteristic pearly white color, which remains almost indelible.

Vaccinal Fever.—The vaccinal fever appears to be less intense in children vaccinated during the first year of life than in adults who have been vaccinated for the first time. It is often absent entirely in cases of revaccination. It has been studied by v. Jaksch,[9] Erich Peiper,[10] and Sobotka.[11] The temperature rises usually toward the

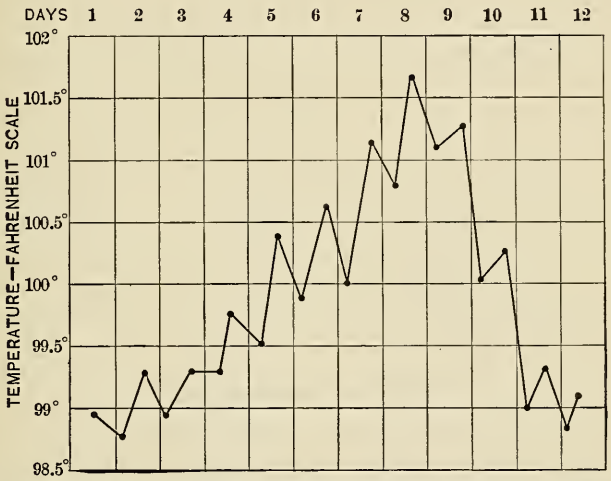

FIG. 12.—Temperature Curve in Vaccina. A schematic chart showing the average obtained by Peiper in nineteen uncomplicated cases. The children's ages ranged from a few weeks to one year. (Surmont.)

fourth or fifth day, sometimes not until the sixth or seventh day, and continues two, three, or four days. The maximum temperature, which is commonly reached on the eighth day, is usually about 39° C. (102.2° F.), occasionally 40° C. (104° F.).

This is the usual course of the temperature when the vaccination has been done with the ordinary precautions, that is to say, after the skin of the child has been washed with some antiseptic solution and when the puncture has been made with a lancet or a needle previously sterilized in a flame. When these precautions have not been taken, the fever may be more intense and may then be accompanied by other symptoms, to which we shall return later.

When the fever is not caused by secondary complications, the nutrition is usually not noticeably interfered with, and there occurs no notable depression in the gradually increasing weight of the child.

Sometimes diarrhœa occurs. L. Perl[12] has reported a unique case in which the child, two and a half years of age, had albuminuria from the fifth to the eleventh day following the vaccination.

Vaccinal Receptivity.

When the inoculation is made with a good virus and in sufficient quantity, and when the patient has not been previously vaccinated nor has had smallpox, the vaccination almost always takes. According to d'Espine[13] vaccinal immunity, that is to say, insusceptibility to the action of the vaccine virus, is met with in less than one per cent. of all cases. Almost everybody, indeed, is susceptible to vaccina. This receptivity exists in children born at the seventh or eighth month and it is found in old age. If we take the ordinary statistics, which are difficult, however, to obtain with sufficient precision, it would appear that vaccinal receptivity is greater than that of smallpox, immunity to variolous inoculation being said to be found in about two per cent. of all cases. But we must eliminate those cases in which there has been a previous varioloid, in which the mother had variola during her pregnancy, etc. If we did so it would probably be found that the figures of one or two per cent. were too high.

Vaccinal Immunity.

We have now to consider how long a time elapses after vaccination before immunity against smallpox is acquired, and how long this acquired immunity lasts. Jenner proved the reality of the immunization by submitting young James Phipps to the test of smallpox inoculation two months after having been vaccinated; it was found that he was refractory to the variolous poison. But how soon after vaccination does this immunity appear? Bryce, the Bousquet vaccine commission, Vetter, and Trousseau have determined this very exactly. They made fresh inoculations every day after the primary vaccination, and found that immunization was definite by the tenth day. Up to that time pustules developed at the seat of the puncture, but these later lesions, said Trousseau, did not reach the size of the first, those being less typical which were the result of the later vaccinations. Thus those of the ninth and tenth days aborted soon after showing a slight degree of inflammation, while after the tenth day there was no specific reaction.

Ten days after vaccination, therefore, the subject has acquired immunity to vaccina, but we have yet to see how the case stands in regard to smallpox immunity. Sacco[14] and the committee on vaccina

employed the same means to determine this as were employed to determine vaccinal immunity. They inoculated children with smallpox on each day following vaccination. As long as the inoculations were not made later than the fourth day after vaccination, says Bousquet, the two eruptions developed simultaneously with the same ease and the same liberty as if each had occurred separately, preserving, however, the relations which ought necessarily to result from the difference of dates. The inoculated variola thus preserves its ordinary characters. But towards the fifth day, and especially after the sixth, while the variolous eruption occurs at the point of inoculation, there is no general eruption nor is there any febrile reaction. The inoculations made on the ninth or tenth day are followed by very poorly defined local lesions, and after the eleventh day the local symptoms fail to appear in the great majority of cases. Thus we see that smallpox immunity is acquired in almost the same time as is that against vaccina.

Let us see what is the process of this immunization. Bousquet showed that it was not interfered with by the destruction of the vaccinal vesicles. On the fourth day after vaccination he destroyed with the lancet and with nitrate of silver the papules which had begun to be visible, but immunization occurred just the same as if the vaccinal eruption had been allowed to follow its normal course. Aimé Martin destroyed the skin with Vienna paste at the point of inoculation before the appearance of any papule, and subsequent inoculations showed that immunity had already been acquired (Surmont[4]). In cows Maurice Raynaud[15] excised discs of skin including the points of inoculation twenty-six hours after the operation. There was no trace of a cutaneous eruption, but the animals were found to be refractory to inoculations made two weeks later.

The local lesion is then not requisite in order that the immunizing substances may be produced in the body, and so it appears that it cannot be the agent, as yet unknown, which is produced in the vaccinal vesicle, that secretes or provokes the formation of the toxin or other analogous product permeating the entire economy. Let us see where this process is accomplished. Chauveau found that the injection of vaccine virus into the lymphatics or veins caused a general eruption without, if proper precautions were taken, the development of any local lesion at the point of injection. It was thus shown that the lymph or the blood might be the carrier of the vaccinal active principle, but it still remained to be determined whether the immunizing principle was elaborated in the lymphatics or in the blood-vessels. The results obtained by various experiments differed among themselves, although the methods employed were nearly identical.

Straus, Chambon, and Ménard transfused into healthy animals 4, 5, and 6 kgm. of blood drawn from a heifer during the stage of full vaccinal eruption, and the animals acquired a perfect immunity. But if the blood was taken four, five, or six weeks after the vaccination, the animal presented no immunity. Contrary results were obtained by Chauveau, Maurice Raynaud, and others, but they might be explained by the fact that the amount of blood injected was insufficient.

The mechanism of this immunization remains still unexplained. We know only that the vaccinogenous substance is present in the blood during the period of eruption, but it is there in comparatively small proportions, since it is necessary to transfuse large amounts in order to produce immunization. We cannot say whether this vaccinogenous property of the blood is due to the presence of the virulent agents themselves or to that of the soluble products secreted by them at the seat of the eruption. The latter, however, seems scarcely possible, since the destruction of the vaccinal lesion at the moment of its appearance does not prevent the subject from acquiring vaccinal immunity.

The immunity acquired by the vaccinated pregnant woman does not always confer immunity against variola or vaccina upon the child. Jenner mentions an instance in which a child came into the world covered with smallpox eruption, although the mother had acquired protection against smallpox through vaccination performed during the latter part of her pregnancy. Telleguen, of Gröningen, according to d'Espine, has reported a similar case. Behm, quoted by Surmont,[4] reports sixty-three instances of successful vaccination of pregnant women, in which only twelve of the children were refractory to the first vaccination; and of these twelve children two were successfully revaccinated, one in the second month and the other at the end of a year. In the Maternity Hospital of Lille, Dubiquet had forty-four positive results in fifty cases of vaccination of new-born children whose mothers had been successfully vaccinated during their pregnancy. The impregnation of the maternal organism with vaccina is therefore not ordinarily sufficient to confer immunity upon the fœtus (Surmont).

We must now determine the *duration of the immunity* conferred by vaccination. For a period following Jenner's discovery it was believed that a vaccinated person was thenceforth always protected against smallpox, but as early as 1805 cases were observed of smallpox occurring in the vaccinated, and during epidemics of variola in 1820 and 1825 instances of this kind were multiplied. The first cases of the sort were swept aside as being not so, but they soon became so numerous that they could not be denied. In order to explain them

two theories were advanced, one that the protective virtue of the vaccine lasted only a certain time, the other that the vaccine deteriorated in the course of successive transmissions through the human organism. Those who adopted the first of these explanations concluded that revaccination was necessary; the partisans of the second theory sought to strengthen the virus from its original source, cowpox.

Husson and Bousquet were the first to recommend *revaccination*. Although in most cases of variola occurring in vaccinated persons the disease appeared in very mild form (varioloid), there were nevertheless some fatal cases, and for this reason Bousquet insisted upon the necessity of revaccination in all cases. It was in Prussia that revaccination was first practised in a way that brought conviction of its value. In that country all soldiers were revaccinated. During the period from 1834 to 1848, out of 425,000 cases of revaccination positive results were obtained in 198,000, or 46.58 per cent. In these fourteen years there were but 77 cases of variola and varioloid in the army, and among them not a single death. In 1843 smallpox was epidemic in Prussia, but in the entire army there were but 12 cases. The results of this experiment could not fail to attract attention of those in other countries, and some years later, at the instigation of the French Academy of Sciences, the same rule was adopted for the French army.

Can we determine the exact duration of immunity, or, in other words, at what age ought we to revaccinate? In order to determine this point Lalagade[16] undertook a statistical study, the results of which are given in the following table:

Ages of those revaccinated.	Number.	Positive results.	Doubtful results.	Negative results.	Percentage of successes.
5 to 10 years	217	19	23	175	8.75
10 " 15 "	324	150	42	132	46.29
15 " 20 "	335	160	17	158	47.76
20 " 25 "	473	238	32	203	50.31
25 " 30 "	208	104	15	89	50.00
30 " 35 "	164	81	14	69	49.39
35 " 40 "	98	26	9	63	26.55
40 " 45 "	95	12	5	78	12.63
45 " 50 "	101	13	3	85	12.77
50 " 55 "	49	5	3	41	10.20
55 " 60 "	66	6	2	58	9.09
60 " 65 "	32	2	1	29	6.25
65 " 70 "	39	4	0	35	10.25
Totals	2,201	820	166	1,215	37.25

This table shows that as early as from five to ten years revaccinations begins to be successful, but in small proportion; that between the ages of ten and thirty-five years the percentage of successful cases

is about fifty, and that after the age of thirty-five years the receptivity rapidly diminishes. It is possible that the number of successful revaccinations, as shown by this table, is even smaller than it should be, for some of the individuals included may have already been revaccinated or may even have had varioloid. The figures are in accord with those obtained from the army statistics, in which we find that the cases of successful revaccinations among soldiers number from fifty to sixty per cent. of the total. In the schools the proportion of successful vaccination varies from fifteen to twenty-five per cent. (Saint-Yves Ménard[17]).

The duration of vaccinal immunity is, however, not absolutely fixed, but varies with the individual. Glogowsky has seen revaccination succeed in children of six years, and Juhel-Renoy has seen children of the same age, who had beautiful cicatrices, take smallpox and even die of it.

The immunity conferred by variola against a second attack is also subject to the same variations. In 1868 I saw a lady at Passy who was suffering from confluent variola, being then thirty-two years of age; in 1871, after the siege of Paris, she had an attack of discrete variola; in 1873, having occasion to vaccinate her niece, I performed the operation on her and was surprised to find that it took perfectly. Thereafter I revaccinated this lady six times at intervals of six months, in the presence of Dr. Lorain, and each time the vaccinal eruption appeared with absolute regularity. In 1876 the lady left Paris and I have not seen her since.

The importance of this question of revaccination will be shown by a few statistics. In Prussia the mortality from smallpox in the year 1835 was 27 per 100,000; in 1872 it was 262. In 1874 vaccination and revaccination became obligatory, and the mortality fell at once to 3.60, and in 1886 it was only 0.39 per 100,000. In 1886 there were 197 deaths from variola in the entire German Empire; in 1887 there were 168, in 1888 there were 110.

Raths[18] presents the following table of the mortality from smallpox in different countries.

Countries.	Population.	Deaths from smallpox.	Deaths from smallpox per 100,000 inhabitants.
198 German cities	10,518,382	42	0.4
15 Swiss cities	489,164	4	0.8
28 English cities	9,398,273	604	6.4
69 Belgian cities	1,910,625	181	9.5
12 Hungarian cities	856,285	102	11.9
52 Austrian cities	2,658,612	1,440	54.2

To this we may add the figures for one hundred French cities of over ten thousand inhabitants in the year 1889:

Country.	Population.	Deaths from smallpox.	Deaths from smallpox per 100,000 inhabitants.
100 French cities	7,449,142	2,623	35.0

Comparing the cities of the German empire with foreign cities for the year 1888, Raths made the following table:

	Deaths.		Per 100,000
Germany—Hamburg, Breslau, Dresden, Leipsic, Magdeburg, Frankfort-on-Main, Düsseldorf, Bremen, Nuremberg, Dantzig, Stuttgart, Chemnitz, Strasburg, Elberfeld, Altona, Barmen, and Stettin had not a single death from variola.			
Berlin	1	or	0.1
Cologne	1	"	0.4
Munich	1	"	0.7
Hanover	4	"	2.7
Königsberg	7	"	4.5
England—London	9	"	0.2
Sheffield	408	"	127.0
Austria—Budapest	13	"	3.0
Vienna	62	"	8.0
Lemberg	27	"	22 0
Triest	254	"	163.0
Prague	741	"	250.0
Italy—Rome	83	"	22.0
Genoa	136	"	74.0
Spain—Madrid	272	"	57.0
Barcelona	506	"	203.0
Roumania—Bucharest	100	"	49.0
Russia—Moscow	23	"	3.0
St. Petersburg	61	"	6.0

In France the statistics published at the request of the Committee on Hygiene by the Minister of Commerce and the Minister of the Interior, for the years 1886-87-88, give for cities of over 10,000 inhabitants an annual mean of 3,260 deaths from variola. The population of the 229 cities of France having over 10,000 inhabitants is 8,575,575; the population of France is 38,218,903, and if the same proportion holds for all France as for the urban population the total deaths from smallpox must be 14,000 per annum.

The logical conclusion drawn from this fact is that revaccination ought to be obligatory. In an address delivered before the Academy of Medicine of Paris on February 25th, 1891, Le Fort opposed this proposition, but in order to refute his argument it is only necessary to quote the following from his paper. Taking as the basis of his figures the epidemic of Sheffield, which I believe with him was one of

the best studied, he says: "Of 18,020 vaccinated persons there were 4,151 who had smallpox, or 23 per cent. Of 736 non-vaccinated persons there were 552 who had smallpox, or just 75 per cent. Of the 4,151 vaccinated persons with smallpox, there were 200 who died, a mortality of 4.8 per cent. Of the 552 non-vaccinated smallpox patients 274 died, a mortality of 49.6 per cent., or nearly half the number of those attacked." Thus we learn from Le Fort's own avowal that in a time of epidemic three out of four non-vaccinated persons contract smallpox, and of this number nearly one-half die; but only one person in four vaccinated contracts the disease, and he has twenty chances to one of recovery.

Le Fort continues: "In 1887 in Sheffield there were 18,121 persons who had already had variola, and of these there were 23 who contracted the disease again, that is to say, a proportion of 1.3 per 1,000. Of 63,354 revaccinated individuals, 75 contracted smallpox, a proportion of 1.1 per 1,000. The proportion among those who had been vaccinated but once was 230 per 1,000. We may therefore believe that revaccination protects as fully as a previous attack of variola. The protective power of vaccina is seen to be even greater when we come to study the statistics of mortality. Since the effects of vaccination weaken with time, if we wish to retain the relative immunity acquired early in life by the primary vaccination it must be reinforced by a revaccination. Although it is not correct to say that revaccination protects one absolutely from smallpox, it is nevertheless certain that it has an enormous protective power, for when it has been recently practised it protects better than an attack of variola passed through at some more or less remote period. The happy influence of revaccination is seen still more clearly if, instead of studying it in the case of one individual, we observe its effects in the case of the entire vaccinated population. To the individual protection is to be added in the case of each vaccinated person the personal protection of his neighbor, and cases of variola will become more rare as the occasions for contracting the disease become more exceptional.

"A vaccinal inoculation, which exposes the individual to no danger when it is practised with the ordinary precautions; which, it is true, does not confer absolute immunity, since the vaccinated person has one chance in four of contracting variola, but which gives him twice as many chances of not contracting it as the non-vaccinated; an inoculation which gives the person receiving it ten times as many chances as the non-vaccinated of not dying from variola if, in spite of the vaccination, he contracts the disease; which therefore gives him twenty times as many chances of escaping death from smallpox

as the non-vaccinated has; an inoculation which, repeated in adult life, protects the individual as thoroughly as a previous attack of smallpox would, is of incontestable benefit."

In the face of this demonstration by Le Fort, the evidence of which was most striking, it would have been useless to furnish new proof to the Academy, but it may not be useless to present to a new audience figures in corroboration of Le Fort's position. From a theoretical point of view, and leaving aside for the moment the methods employed, we may say of a population in which every individual has been revaccinated that it is absolutely protected from an epidemic of smallpox. There might be a few cases of varioloid but there would be no epidemic of variola.

Professor Arnould, of Lille, has given the following figures: In Germany, in 1890, there were only 32,286 non-vaccinated persons, and of the vaccinated only 9,704 not revaccinated. The deaths from variola in 1886 were 197, 168 in 1887, 112 in 1888, 200 in 1889, and 58 in 1890. In Berlin there were only 3 deaths from smallpox in this latter year. In 1891 there were but 40 deaths from variola in the entire German Empire. The number of deaths from this disease in France was 56 times greater, in Austria 60 times greater, and in Italy 97 times greater.

Table showing the deaths from smallpox per 100,000 inhabitants in five German cities since the law making vaccination obligatory has been in effect (Hervieux: "Rapport sur les Vaccinations," 1895).

	Berlin.	Breslau.	Hamburg.	Munich.	Dresden.
1871	632.5	356.7	107.5	88.9	360.2
1872	138.6	282.5	95.2	6.5	85.2
1873	11.2	13.7	0.8	2.9	13.1
1874	2.4	0.8	0.5	1.0	4.3
1875	5.1	....	....	....	2.5
1876	1.8	....	1.8	0.5	0.5
1877	0.4	0.7	1.2	....	0.9
1878	0.7	1.5	0.2	0.9	....
1879	0.7	0.3	....	....	1.8
1880	0.8	0.7	....	....	3.6
1881	4.7	1.1	2.2	10.3	2.6
1882	0.4	3.2	0.5	2.9	1.3
1883	0.3	8.3	....	....	0.8
1884	1.6	....	....	....	0.4
1885	0.4	....	0.9	5.4	1.3
1886	0.07	....	3.6	0.8	....
1887	0.2	0.6	0.6	0.4	0.4
1888	0.3	....	....	0.7	....
1889	0.16	....	....	0.4	....
1890	0.2	0.3	....	0.4	0.8
1891	0.4	....	....	....	?
1892	0.1	0.3	0.7	0.8	?

During the last four years, since the report of all contagious diseases has been made obligatory and since the service of disinfec-

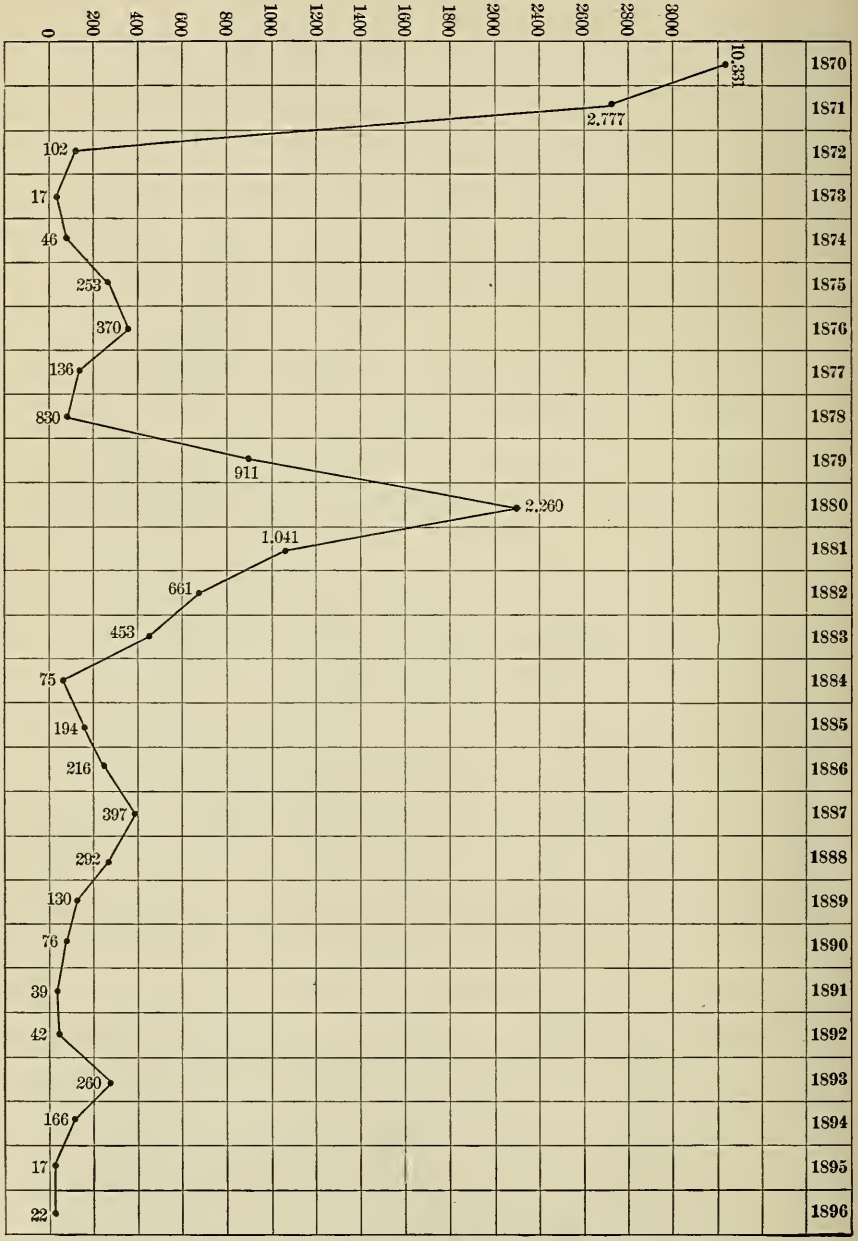

FIG. 13.—Chart Showing Mortality from Smallpox in Paris from 1870 to 1896.

tion has been organized in Paris, the number of deaths from variola has fallen greatly, and the disease now numbers scarcely fifteen or twenty victims a year. The accompanying chart shows the mortality from smallpox in Paris during the years 1870–96.

I have said above that, when it was discovered that a single vaccination did not always protect a person for life from an attack of smallpox, the hypothesis was ventured that in its successive passage through the human organism vaccine virus degenerated and lost a part of its activity. The proofs advanced by the supporters of this theory are not very conclusive. They have compared the description of the vaccine eruption given by Jenner with what is observed to-day. But this comparison is not very demonstrative, for if we observe two children vaccinated with the same virus and at the same time, we see that the reaction is very probably not of equal intensity in both. The only proof advanced by those who believe in the degeneration of the virus is that revaccination is now regarded as necessary, while formerly a single vaccination was deemed sufficient. The truth is, however, that this belief was incorrect, and in fact there is nothing less proven than that the vaccine loses its protective power in passing through several generations in the human organism.

Anomalies in the Vaccine Eruption.

The description of the eruption which we have given above is certainly a little schematic, for the reaction may vary considerably in intensity even in children. It has been said that the eruption following a successful revaccination is less frank in character than that of a primary vaccination, but this is contrary to the general testimony of those who have studied the subject and contrary also to my own experience. When an adult is revaccinated with success the inflammatory phenomena are in general more intense than those which accompany vaccination in the child. The vaccinal papule has not always the regularity, the rounded, flattened form that we see in children, but often the peripheral swelling, that of the subcutaneous connective tissue, is more marked, the tumefaction of the axillary glands is more pronounced and more painful, and sometimes even there are pains radiating into the shoulder and down the arm. An inability to use the arm for several days may be the consequence of this rather intense reaction, and therefore it is advisable when revaccinating soldiers, laborers, and others who are more or less dependent upon the free use of their arms to perform the operation on one arm only instead of the two.

Whether the case be one of primary vaccination or of revaccina-

tion, the vaccinal pocks do not always develop equally; some are large, others abortive, and sometimes one or two may be developed later than the others. A case of this kind reported by Wichen is, however, rather exceptional. He made eight vaccinal insertions in a child one year old, and of these three developed normally; the other five gave rise to pocks on the twelfth day, and these attained their maturity in three days.

The period of incubation is that which appears to be subject to the greatest variations. Its normal duration is three days, but Hervieux says he has often noticed a little red circle announcing the appearance of the papule by the second day. In other cases, for some unknown reason, instead of being shortened the period of incubation is unduly protracted, instances being recorded in which the papule did not begin to show itself until the seventh, eighth, tenth, fifteenth, twentieth, or even thirtieth day. In certain cases the physician has been led to believe that the vaccination has failed, and on making a second inoculation has seen the eruption of both vaccinations develop simultaneously. The cases of Frébault, cited by Bousquet, and those of Rilliet and Barthez remain unique and still await confirmation or an explanation. Frébault claims to have seen a relapse of vaccina occurring immediately after the fall of the scab, and Rilliet and Barthez relate a similar occurrence several months after the primary eruption.

The irregularities which we have just noted are not of great importance, for they do not in any way compromise the success of the vaccination. We shall now consider some variations which are more significant and which have been the occasion of some interesting discussions.

Vaccinoid.

When physicians first began to practise revaccination they noticed that the pock often presented characters which differed greatly from those of the primary normal vaccine eruption. They gave to this eruption the name of false vaccina, and without explaining it satisfactorily were content to regard it as in general insufficient to secure the protection of the individual such as would have been obtained by a normally developing eruption.

This theory was combated by several acute observers, notably by Trousseau and Dumont-Pallier in 1860. They looked upon this false vaccina as bearing the same relation to true vaccina that varioloid bears to variola. They believed that it developed, like varioloid, upon a soil which was not absolutely sterile, yet which was unfit for the complete development of the inoculated virus, and they justly

proposed to substitute for the term false vaccina, which might be misinterpreted, that of vaccinoid, a condition which was analogous to varioloid and possessed an immunizing power similar to that of this affection. Hervieux has fully accepted this view, and to him belongs the credit of having demonstrated before the Paris Academy of Medicine in 1893 that vaccinoid transmits by inoculation true vaccina, and that consequently, like vaccina, it confers immunity to smallpox.

The following is the description given by Hervieux of vaccinoid. It does not begin, as has been said, immediately after the inoculation, but there is an incubation period of about twenty-four hours on the average. There are three types of vaccinoid, dependent upon the extent to which the weakening of the immunity has advanced:

1. At the point of inoculation there appears a pink papule, hardly at all elevated above the surrounding integument, and without any areola; it disappears at the end of a few days, leaving no scar.

2. There forms an acuminate papule, larger than that seen in the first type of vaccinoid, redder, more distinctly visible, surmounted by a little vesicle at its point, surrounded by a faint areola, and leaving after desiccation a little scab which falls soon without the formation of a cicatrix.

3. The vesicle is more distinct, the areola is more pronounced, the scab is larger and more adherent and leaves behind it a cicatrix, which, however, disappears in the course of time.

These evidences of vaccinal action are usually accompanied by considerable itching, but there is no fever, and the process confers immunity. Although vaccinoid is seen ordinarily in those who have previously been vaccinated or who have had an attack of variola, Cadet de Gassicourt [19] claims to have observed it in children following a primary vaccination.

Vaccina without Eruption.

In 1825 Dr. Treluyer in company with five other physicians of Nantes vaccinated sixty children. By the second day these began to suffer with malaise, headache, and chills, and on the third day fever appeared; but no vaccinal vesicle appeared at any time during the course of these general symptoms. The children were subjected to another inoculation, but this was followed by no general or local symptoms whatever. Smallpox was then prevailing at Nantes and these children were exposed to it, but none of them took the disease with the exception of two who had not presented the general symptoms observed in the others. Finally, in order to make this observation even more conclusive, five of these children were inocu-

lated with smallpox virus, but none of them contracted variola, the only result of the operation being a slight indisposition lasting about a week. The physicians who noted this unusual occurrence, that is to say, the acquisition of immunity without a vaccinal eruption, regarded it as analogous to the febris variolosa sine variolis of Sydenham, to the *scarlatine fruste* of Trousseau, and to other instances of an exanthematous disease occurring without the characteristic exanthem.

Chauveau has obtained the same result experimentally. He first injected vaccine virus into the subcutaneous cellular tissue of heifers, and found that the animals had acquired immunity although there had been no vaccinal eruption. He then practised injections in man, taking the precaution not to inoculate the individual locally at the point of entrance of the needle. There formed under the skin a hard swelling which disappeared slowly; there were glandular enlargements and a rather sharp febrile reaction, but no cutaneous eruption. Later inoculations showed, however, that the persons experimented upon had acquired immunity.

Surmount remarks justly that these cases of vaccina without eruption are exceedingly rare, and that the physician should not trust to the immunizing power of an inoculation when the vaccina has been irregular in its symptoms; therefore, in the absence of a normal vaccine eruption, a second attempt at vaccination should be made.

Generalized Vaccina.

Instead of remaining limited to the points of inoculation of the virus, the eruption may appear on other portions of the skin which have been untouched by the lancet. There are two forms of this generalized eruption which differ greatly from each other, especially in their pathogenesis. In the first form the skin is disposed to inoculation everywhere because it is the seat of an eczema or of some other dermatosis, and the vaccinated person may easily carry some of the secretion from the original vaccine vesicle to other parts where the epidermis is wanting, and thus secondary inoculations are made. This dissemination is facilitated by the fact that the vaccinal eruption is often accompanied by an intense pruritus, and that the parts of the body where the eczematous eruption exists are also the seat of itching. The diagnosis of this form is easily made, because the vaccinal vesicles are often ruptured, and around the secondary vesicles we may see under the glass or even with the naked eye the marks of scratching, and we also see on the fingers of the patient a paronychia which resembles more or less closely the vaccinal eruption. The secondary

eruptions are, furthermore, of later development if we compare them with the pock at the point of primary inoculation.

Any other preëxisting lesion of the skin exposes the patient to vaccinal eruptions on the parts which it occupies, and it is among occurrences of this sort, the autoinoculations, that we must place the case reported by Bergasse. A child having a Biskra button in process of cicatrization on the left ala nasi was vaccinated on the left arm. When Dr. Bergasse saw the child again on the ninth day after the operation, the left side of its face was covered with upwards of twenty vaccine papules similar in appearance to those on the arm. The general symptoms were grave and the child's condition did not begin to mend until the fourth day.

In the first form there is no difficulty in explaining the generalization of the vaccina. In other and much more rare instances the generalization would seem to be due to the transportation of the virus in the blood current. I have never seen an instance of this sort, but will quote the description of Jeanselme[20] based upon cases observed by himself and by Damaschino and Surmont. "An important symptom, the uniformity of the elements of the eruption which are all of the same age, distinguishes this variety from vaccina generalized by autoinoculation (Damaschino). The eruption is sometimes contemporaneous with that occurring at the points of inoculation, but more frequently it arises secondarily towards the seventh or eighth day. The secondary elements develop more rapidly than the primary eruption, and in the course of a few days the two become identical in appearance; by the tenth to the thirteenth day their development is complete; then they diminish in size, and disappear toward the sixteenth day, leaving no other traces than a slight macule which becomes rather rapidly effaced. The eruption may be discrete, coherent, or confluent; in the latter case the general symptoms and the fever are at their maximum and death even may occur, but ordinarily the prognosis is not so grave. This form, which is more rare than that following autoinoculation, may be observed after vaccination or revaccination, but especially after accidental inoculation with cowpox or horsepox (Bouley's case). Individual predisposition seems to play the principal rôle in its genesis. Some of the older cases would seem to show that generalized vaccina may follow absorption of fresh vaccine from the digestive tract (Richard, 1809, and Etienne), or even that of the ordinary dried virus (Cazalan, 1809). It is often difficult to disabuse one's self of the idea of an autoinoculation in reading the reports of cases cited in support of this conception."

It is possible in these cases to assume that the lancet holding the virus on its tip has been inserted a little too deeply and has pene-

trated a lymphatic or a venule of appreciable size, and thus the experiment of Chauveau, to which we have referred above, has been accidentally repeated.

Coincident Eruptions.

Various eruptions, called indirect vaccinal eruptions by Hervieux, may appear coincidently with the normal eruption of vaccina.

Erythema.—We may distinguish a first group characterized by the appearance of more or less generalized erythematous patches to which have been given the names erythema, rash, and roseola. These red spots make their appearance during the height of the vaccinal eruptions from the ninth to the eleventh day. This observation of Hervieux has been confirmed by other observers, notably by Ausset.[21] Roger has observed the erythematous spots as early as the third day, while Behrend has seen their appearance delayed as late as the eighteenth day.

When these erythematous patches become more generalized they are usually called by the name of roseola. This appears first around the vaccinal vesicles and then spreads to the neck and arms and sometimes covers the whole body. It lasts two or three days, but generally produces no constitutional symptoms. It does not terminate in desquamation. It may assume the appearance of the eruption of measles or scarlatina, and sometimes takes on the characters of a papular eruption resembling polymorphous erythema (Behrend).

Bousquet regarded these eruptions as independent of the vaccina, and believed that their appearance was a mere coincidence. Depaul thought their occurrence was due to some personal idiosyncrasy. Bonnerie believed that the rash was due to some impurity in the vaccine virus. Behrend compares these vaccinal eruptions to drug eruptions. The latter explanation seems to me to be more reasonable than the others. In reading the accounts given by different authors we are reminded now of infectious polymorphous eruptions, again of eruptions following the ingestion of certain medicaments, and especially of those following the injection of the antitoxin of diphtheria.

Whatever may be the pathogeny of these eruptions, they are benign, but they nevertheless ought always to be studied with care, and they should serve to remind us of the possibility of some other infection, especially of syphilitic roseola or of a concomitant scarlatina, measles, or the like.

Vaccinal Miliaria.—Some writers have also described an eruption which they have called vaccinal miliaria, but in its objective features this evanescent eruption, appearing in successive crops, would recall

rather the sudamina occurring in the course of certain infectious diseases. As in the case of the eruption resembling polymorphous erythemas, it is difficult not to think of the possibility of an infection. This form of eruption is of no more grave character than are the erythemas just described.

Vaccinal Eczema.—In those who are predisposed, especially in scrofulous children, vaccination very frequently causes an eruption of eczema. This usually surrounds the vaccinal vesicles and remains limited to these parts, but sometimes it becomes generalized, and may even recur in successive attacks, presenting then all the ordinary characteristics of eczema in one or other of its numerous varieties in the adult or child. There is really no special vaccinal eczema having characteristics of its own, but the eruption is simply one of eczema which has been provoked by the interference with health caused by the vaccination.

Pemphigus occurs very rarely as a complication of vaccina in children, and when it does occur it has no special characteristics. Attempts at inoculation with the serous fluid contained in the bullæ have never given any positive results. The eruption occurs almost exclusively in debilitated and rachitic children. It lasts several days generally and is quite readily curable. Its appearance in young children after vaccination should make us suspect the existence of hereditary syphilis.

Diday has observed an eruption of *herpes* following vaccination, but this may have been a simple coincidence. Chambard is said to have seen some cases of *psoriasis* arising under the same circumstances.

Buruleaux has reported a case of *hemorrhagic vaccina* terminating in death, and instances of *purpura* have been observed in the subjects of hæmophilia and in debilitated children.

Secondary Infections.

The accidents which we have just been considering are due in general to some personal predisposition; some, such as the erythemas, probably to infection or poisoning. We have now to study those which are certainly due to infection.

Phlegmons.—Among instances of this sort we have to note simple or diffuse phlegmons, abscesses, cases of angioleucitis and of adenitis. These accidents have as their point of departure the region in which the inoculation has been made. They have as their cause infection of the vaccinal vesicles by pus microbes, the introduction having been accomplished either by an unclean vac-

cinating instrument or at a later period by contact with soiled clothes or the hands.

Cases have been reported of *gangrenous vaccina*, in some instances fatal, due very probably to infection in a similar manner (Hutchinson).

Erysipelas was formerly one of the most common complications of vaccination, but since we have come to know more of the pathogenesis of this affection its occurrence has become much more rare. Its cause is to be found in the use of an unclean instrument or in the absence of antiseptic precautions during vaccination or the evolution of the vesicle. According to the time when infection occurred it may appear on the second day of vaccination or at any time during the evolution of the eruption. Among debilitated children erysipelas is a grave complication. Rauchfuss has noted a mortality, in the foundling hospital at St. Petersburg, of sixty-seven per cent. in cases of wandering erysipelas, and one of seventeen per cent. in cases of localized erysipelas. Actual epidemics of the complication have been described. Secondary contamination of this kind ought no longer to occur, and indeed it has become happily so rare that in 1877 Lotz was able to collect only two cases of death from erysipelas in 1,252,554 vaccinations.

Septicæmia has been occasionally, though rarely, observed. Surmont reports the following: At Grabnick (1878) fifty-three children were infected through the use of some old virus which had been exposed to the air for a long time; some of the children had generalized eruptions resembling scarlatina or measles, others had erysipelatous symptoms or abscesses, and fifteen of them died. In two cases the autopsy showed that death was due to septicæmia. The vaccine was in a state of decomposition and contained septic bacteria (Pincus[22]). At San Quirico d'Orcia (1879) near Rome, similar cases of erysipelatous fever, abscesses, and death were observed following the employment of vaccine taken from pustules which had been removed seven days previously.

Twelve years ago the writer was commissioned in company with Pasteur and Proust to determine the responsibility incurred by the physicians who performed vaccination under the following circumstances: On March 13th, 1885, Dr. A., of Asprières, vaccinated forty-two children; the next day six of them were dead, and all the others were ill, some of them very dangerously so. In our investigation we were enabled to trace the vaccine back through five generations and to determine that it was by employing a virus originally good, but which gave rise successively to accidents, at first of slight gravity then more and more serious, that the preparation was made for the

final disaster. The first vaccination was made by Dr. C. with a tube of animal vaccine, on February 16th. The subject vaccinated (there was but one) had a magnificent umbilicated eruption. In the second series twenty children were vaccinated by Dr. C., on February 22d or 23d, with virus taken from the first child. Nothing especial was noted beyond a little inflammation surrounding the vesicles in two or three of the children. One of these served as the vaccinifer for the third series. The third vaccination was made by Dr. C., on February 28th or March 1st. The number of the vaccinated could not be ascertained. Three of them, however, presented abnormal symptoms. V. was reported to have had a fever exceeding in duration that of the normal vaccinal fever, and the pustules appeared sixty-two hours after the vaccination. In B. the pustules appeared forty-eight hours after the vaccination. D., a girl fourteen years old, had an abscess of the arm. The fourth vaccination was practised in March 7th by Dr. C. The vaccinifers were the above-mentioned V. and B., who had had an abnormal vaccine eruption in that it had appeared in the third and second day respectively. Two girls, Clapier and Bessous, were vaccinated with virus taken from a pustule which had opened the evening before. The mother of the Clapier child testified: "On March 7th last my little girl, one year old, was vaccinated at Montbazens by Dr. C. The vaccine was taken from two little girls, aged about three and eight years respectively. The operation was performed about one o'clock in the afternoon, and that very evening fever appeared and the child did not sleep that night. The following day I showed my child to Dr. A., who thought that the vaccination had taken very quickly, and he said that instead of waiting eight days in order to vaccinate other children from this one he would do so the following Friday. I noticed nothing extraordinary about my child except that the vaccination had taken so very quickly. The restlessness lasted about two days, but the child was not sick, and had neither diarrhœa, vomiting, nor convulsions." Mrs. Bessous furnished the following information in her deposition: "Dr. C. vaccinated this child on March 7th. The virus was taken from two children of three and eight or nine years respectively. One of the children had already furnished some vaccine that morning, but one of the pocks had not been opened; in the other child all the vesicles had been cut. Dr. C. gave to my child as well as to my neighbor's girl vaccine from the pock which had not been opened as well as from the ruptured one. The vaccine fever appeared during the night, and the following day I made the remark that the vaccination had taken well. My child was not ill, but had a slight diarrhœa though no vomiting; the next day the child went out; she furnished no vaccine

to other children. It was the Clapier child who was the vaccinifer in the fifth series.

The fifth vaccination was made on March 13th by Dr. A., who vaccinated forty-two children on that day, of whom four died the next day and one the day following that; a sixth child also died, but we know nothing of the circumstances of that case. Almost all of those vaccinated were more or less ill. The following is Dr. A.'s deposition: "I took this vaccine from little Eugénie Clapier, of Asprières, aged twelve or thirteen months, who was a healthy child and whose parents were also sound. She as well as the little Bessous child had been vaccinated on March 7th by Dr. C., who had taken the vaccine for them from another child. I noticed that the incubation period of the vaccina had been very short in both children, for usually it is only after nine days that the virus becomes fit for inoculation, but in this case it was imperative to give it as early as the sixth day, for it had already begun to desiccate."

Concerning the results of this vaccination we were able to obtain fairly definite information as regards five of those who died and five who recovered.

I. Death of the Crouzat child; deposition of the mother: "I had my daughter Angèle, about two years old and very robust, vaccinated at Asprières by Dr. A. on March 13th. She was the first who received the vaccine. On the morning of the 14th she had a slight chill. I did not expect that the vaccine would take effect so soon. The child began to have diarrhœa and vomiting, and it died on the 15th of the month towards six o'clock in the morning."

II. Death of the Fabre child; deposition of the mother: "On March 13th last, towards nine o'clock in the morning I had my daughter Pélagie, thirty-two months old and very robust, vaccinated by Dr. A. at Asprières. That evening the child went out for a walk, she took her supper as usual, and I put her to bed about eight o'clock. An hour and a half afterward she awoke and vomited what she had eaten; the vomiting was repeated three or four times. Towards one o'clock in the night she was taken with diarrhœa. The next morning she was thirsty; she rose about six o'clock and walked around as usual. Towards eight o'clock she was taken with giddiness and uttered a plaintive cry two or three times; then she had convulsions and died about half-past nine that morning. After her death I noticed that her legs were covered with purple spots."

III. Death of the Laumont child; deposition of the mother: "On the day they vaccinated children at Asprières I took my little three-year old boy there. Dr. A. vaccinated him about ten o'clock in the morning. After coming home the child played about as usual out-

doors. He got his supper a little early that evening, and when he was put to bed, about seven o'clock, he felt like vomiting. I gave him some tea, which he did not care for, and then he vomited three or four times, throwing up his supper; he had a troublesome diarrhœa during the night. He died about ten o'clock the next morning. His face did not appear changed, but the legs and thighs were covered with black spots. I noticed no other signs of decomposition. The child had not been sick before this."

IV. Death of the Sounillac child; deposition of the mother: "My mother had my little girl Marguerite, two and a half years old, vaccinated at Asprières by Dr. A. on March 13th, about ten o'clock in the morning; the child was strong and robust. In the evening the child went out for a few minutes, the temperature of the air having fallen a little at that time. That same evening at about seven o'clock she asked me to take her on my knees, saying that she was tired. Almost immediately she began to vomit, at first some bread she had eaten and after that glairy matter. During the night she was very restless and had considerable diarrhœa. The little one died at nine o'clock in the morning. After death her face changed a little and there were purplish spots on the neck, arms, and legs."

V. Death of the Gratacap child; deposition of the mother: "I had my boy vaccinated by Dr. A. on March 13th at about eleven o'clock, that is to say, among the last of those who were vaccinated. He was three years and a half old, and was a very strong child. The day was rather cold, but my boy was well wrapped up and went out as usual. Towards eleven o'clock at night he felt an inclination to vomit but did not do so. During the night he had two large diarrhœal passages and was much exhausted the following morning. He had a few convulsive attacks and died at four o'clock. After death his entire body, with the exception of the arms and face, became black."

The symptoms of those who did not die were very similar to these just described and came on also at about the same time. The ages of the vaccinated children varied from three months to three years. It is worthy of note that it was not the youngest children who died. The symptoms appeared from four to sixteen hours after the vaccination, the usual period being between nine and ten hours. In all there was fever, appearing at the latest eighteen hours after the vaccination; in those who recovered it lasted from two to four days; nearly all had vomiting followed by diarrhœa, and some had convulsions. Four of the children died at the end of about twenty-four hours; one, the Crouzat child, the first one vaccinated, lived for forty-five hours after the operation.

The children who recovered had local symptoms resembling in no

respect the eruption of vaccination. In all, from the first day, an intense redness over an area the size of a fifty-centime piece (a silver ten-cent piece) surrounded the point of inoculation. There was a discharge of a serous or seropurulent fluid on the first day or by the third day at the latest. Cicatrization was slow. In all of the children a local and generalized impetiginous eruption followed the inoculation. There is nothing in this description resembling the normal course of vaccina.

We see from this history that, starting from the third series of vaccinations, the vaccina did not follow its normal evolution, and that the vaccinifers had eruptions which would cause a doubt whether the two children in the fourth series had been inoculated with vaccine at all. Thus the symptoms became aggravated at each new transmission until they terminated in the disaster of March 13th.

These symptoms could be compared to nothing but those of acute septicæmia. The only thing in human pathology which they resembled was a dissection wound produced by inoculation in a crack or wound of the skin with pus from a subject dead of some septic affection such as puerperal peritonitis. In this case the symptoms burst forth in all their intensity without the necessity of successive transmissions of the septic germs. In the vaccination cases, however, it would seem that the virulence noted first in the third series went on increasing in each generation, it being evident that the virulent germs were strengthened in the successive cultivations.

Actual epidemics of *impetigo* and *ecthyma* have been reported in recent years in Germany. They were sometimes of considerable gravity and caused the death of some of the children. Among these epidemics we may mention that at Rugen in 1885, at Sédow in 1885, at Eiderstedt in 1886, and at Elberfeld in 1887.

Some writers have made the statement that these accidents are never observed except as a consequence of animal vaccination, but this is an error, as witness the Asprières cases.

Ulcerative vaccina occurs under two distinct forms. In one the ulcers develop on one child only, in the other there is a real epidemic. When the ulcer forms on the arm of one child only, the physician will think at once of syphilitic chancre. Indeed it resembles greatly a chancroid or true chancre, whence the names of chancriform vaccina, vaccinal pseudochancre, etc. The vaccinal ulcer differs, however, from the syphilitic sore in the time of its development, appearing on the seventh or eighth day (Pinard's case) or from the twelfth to the fifteenth day (Fournier). All or nearly all of the points of inoculation become ulcerated. The ulcer is the size of a fifty-centime piece, and it is accompanied with lymphangitis, œdema of the limb,

impetiginous and ecthymatous eruptions, and painful adenopathies. The child is in a typhoid condition. Cicatrization occurs only by the end of two or three months, and the resulting scar is permanent and often deforming.

Epidemic ulcerative vaccina differs from the preceding only in the fact that it affects a number of children. The epidemic which has been the most carefully studied is that of Motte-aux-Bois, described by Decouvelaere, Hervieux,[23] and Leloir.[24] The vaccinifer was a child nine years of age, of fine appearance, healthy and robust. The eruption on this child had followed a normal course and cicatrization was completed at the usual time. Forty-three children of different ages were vaccinated in three places on one arm only. Each had three papules, appearing on the second or third day, which became rapidly inflamed, greatly enlarged, and gave place between the tenth and twelfth days to three ulcers varying in size from the diameter of a fifty-centime piece to that of a franc or a two-franc piece (a dime to a half-dollar. The borders were sharply cut out, suppuration was abundant, œdema was very pronounced, and there was axillary adenopathy, but the general health was scarcely affected. None of the secondary symptoms of syphilis appeared.

The affection was an inoculable one, since the ulceration occurred at each point of vaccination, and even the mother of one of the children presented an ulcer of similar appearance on the lower eyelid. Leloir believed that the lesions on the arm of the vaccinifer became invaded at an early period by the staphylococcus pyogenes. The complication is a serious one, and the consequences might be grave.

Vaccinal Syphilis.—This is a subject which has greatly occupied the attention of medical men for the last quarter of a century, and although the substitution of animal vaccination in place of the arm-to-arm method has removed the danger in great measure, the possibility still exists and the question retains its interest as regards diagnosis. From the very beginning of vaccination cases occurred in which popular opinion accused the operation of having inoculated other diseases, and especially syphilis, along with the vaccina. Rowbey in England (1810), Monteggia in Milan (1814), and Marcolin in Milan (1823), all expressed the belief that the vaccinal vesicle might contain the virus of syphilis as well as that of vaccina. Troja and Galbiati of Naples (1810), being convinced that some vaccinated patients were affected with diseases from which they had not previously suffered, instituted a service of animal vaccination. These facts and others which we shall mention below were met in France by the two following arguments: According to the opinion of Husson, Bousquet, and Steinbrenner vaccine virus remains always pure and

cannot be mixed with any other virus. In support of this opinion they adduce certain apparently very conclusive experiments. They performed vaccination, intentionally taking the virus from syphilitic children, and the subjects vaccinated did not show any symptoms of syphilis. Furthermore, according to the teachings of a school which were generally accepted until about 1860, the primary sore alone can give syphilis, it being impossible to transmit the disease by inoculation with the secondary products. "Chancre arises from chancre and alone can reproduce it" (Ricord). Resting upon these facts which had withstood the assaults of many discussions, the French physicians regarded the published cases of alleged vaccinal syphilis as merely the impotent assaults of the detractors of vaccination. But when experience had disproved the law of Hunter and Ricord, and especially when accounts were published of veritable epidemics of vaccinal syphilis, opinion began to change, and when Viennois[25] published his work on the transmissibility of syphilis by vaccination, a new period opened in the history of vaccination.

Depaul[26] introduced the question in the Paris Academy of Medicine in 1865, and the discussion was very animated. The contest arose again in 1869, and it was only in 1870 that the last opponents of the possibility of this mode of transmission of syphilis disappeared.

Certain of the cases of alleged transmission of syphilis may be rejected as being merely instances of the declaration of a latent syphilis brought out by the operation of vaccination; such were cases reported by Friedenger, Bamberger, Ceccaldi, and Whitehead. We shall refer briefly to two of the best known of these epidemics of vaccinal syphilis.

First observation of Gaspard Cérioli, in 1821.—A little girl, three months old, a foundling, was inoculated with vaccine taken from another child who was healthy at the time and remained so. Vesicles developed in a regular manner and from them virus was taken for the vaccination of forty-six children. Six of the latter had normal vesicles with the fluid of which one hundred children were vaccinated, none of whom showed later any symptom of syphilis. In almost all the others there appeared at the points of inoculation ulcers covered with scabs, or indurated ulcers. These lesions manifested themselves at the time when the vaccinal scabs fell off. Later appeared ulcers on the mouth and genital organs, scabby eruptions on the hairy scalp, copper-colored spots on the body, etc. The osseous and glandular systems were also involved. The disease was also communicated to the mothers and nurses of the affected children. Admitted to hospital, the patients were treated by mercurial inunc-

tions and bichloride of mercury internally. Nineteen of them died, the others recovered more or less promptly. All the infected mothers recovered.

Epidemic of Rivalta.—Towards the end of May, 1861, Dr. Coggiola vaccinated a child, Chiabrera by name, who had been infected with syphilis from the breast of a woman who had nursed it accidentally. This circumstance was not known, however, until it was revealed by the searching investigations of Dr. Pacchioti. This child served as vaccinifer for forty-six perfectly healthy children. This was on June 2d, and on the 12th of the same month seventeen other children were vaccinated with virus taken from one of the first forty-six children, by name Manzone. The entire number of the vaccinated was thus sixty-three, and of these forty-six were infected with syphilis, thirty-nine of the first series and seven of the second.

The first symptoms of syphilis appeared on the average on the twentieth day after the vaccination, the extreme limits being ten days and two months. The ulcers on the arm made their appearance either during the cicatrization of the vaccinal eruption or after that was completed. After this came on the general eruption.

An inquiry was undertaken October 7th, when it was ascertained that seven of the children had died, the disease not having been recognized; there were no further deaths after the institution of specific treatment. At the time they were discovered fourteen of the children were progressing favorably toward recovery and three were in a dangerous state. All the children who could be found had had symptoms of syphilis and had communicated the disease to their mothers and nurses and these in turn to their husbands, so that the disease had made frightful progress in the community.

Other cases of this kind followed each other, and in 1863, when Devergie reported to the Paris Academy of Medicine the case of a lad, fifteen years old, who presented the secondary symptoms of syphilis six weeks after having been vaccinated, Ricord remarked: "The observations have multiplied, the proofs have accumulated, and we can no longer hesitate to accept as certain this mode of transmission. One member only of the Academy (Bousquet) refused to accept this view, saying: "Husson, our glorious predecessor, never saw any cases of the kind, I have never seen any, Depaul himself has never seen any, and I am glad to be able to tell him that he never will see any." Unfortunately two years later this prediction of Bousquet was cruelly falsified by a case occurring at the Academy under the eyes of Depaul, whose report of the incident is as follows: [27]

"On August 10th, 1865, a colleague in Paris sent to the Academy to be vaccinated his nephew, a young man twenty-seven years of age.

I could not go to the Academy that day and the vaccinations were performed in my absence. I had no thought but that everything had occurred normally, when I was informed that this young mar was affected with vaccinal syphilis. He was treated by Millard, Hardy, and Ricord, and made a slow recovery. Filled with anxiety for the others who had been vaccinated at the same time, I instituted an inquiry. I learned that vaccine had been taken that day from two vaccinifers, and several children and some soldiers had been vaccinated. Thanks to the information obtained by Lanoix, I was able to trace the children who had been vaccinated and had acquired syphilis, two of whom died. As to the soldiers one day I received a letter from Val-de-Grâce asking me to come to see some soldiers who were suffering from vaccinal syphilis. Three of them had characteristic ulcers, adenopathy, etc. I found on interrogating them that they were three of the soldiers who had been vaccinated at the Academy on the same day as the young man and the children mentioned above.

"The first of the vaccinifers who had furnished the virus that day was perfectly healthy, and it was he who had given the vaccine to most of the soldiers. I could not see the other, for he had died the day after furnishing the virus for vaccination. When I entered the house his mother said (I quote her words literally): 'Could he have given the disease to the others?' This woman had put her child out to nurse, but had had to take it back, as the nurse was suffering from a venereal affection. The child had a macular eruption, glandular swellings, and ulcers in the groins and on the genitals."

The possibility of the transmission of syphilis by arm-to-arm vaccination could no longer be doubted. It remained to determine the prophylactic means, and we shall see later how this was done. But first let us study how the contamination of the virus occurs.

First of all it is certain that in the immense majority of cases a syphilitic vaccinifer does not give syphilis to the vaccinated. The old experiments of Husson, Bousquet, and many others are a sufficient proof of this statement. The observations which we have related above also confirm this, since in every instance there were always some who escaped the syphilitic infection. How are we to explain this immunity for some and this contagion for others?

When we perform an arm-to-arm vaccination the lancet is charged with vaccine and usually also with a small quantity of blood, and especially when several children are vaccinated from the same vesicle the latter almost always bleeds more or less. Examination of the vaccine virus under the microscope will almost always show blood corpuscles even when there is no appearance of blood to the naked

eye. Since, therefore, it is almost impossible not to have blood mixed with the vaccine, we must ascertain whether the contagion may occur through one or the other of these fluids. Experience has shown over and over again that syphilis may be communicated by inoculation with the blood of a syphilitic subject apart from any question of vaccine virus. Thus, to cite only one instance which suffices to prove the fact: In 1860 Pellizari,[28] of Florence, in the course of a lecture, stated his belief that the vaccine alone cannot transmit syphilis and that vaccinal syphilis occurs solely through inoculation with syphilitic blood. After the lecture two of his auditors, Drs. Billi and Sebastien Testi, asked Pellizari to experiment upon them with the inoculation of syphilitic blood. The professor objected but they insisted, and the inoculation was made; the result was negative. The following year after a lecture on the same subject, three physicians, Bargioni, Rosi, and Passigli, were inoculated, and Bargioni alone acquired syphilis. The woman from whom Pellizari took the blood was twenty-five yeas old, pregnart six months, and had had the primary sore fifty days before. She had large confluent mucous papules, which secreted abundantly, on the genitals; one of these corresponding in location to the primary sore had a frankly indurated base. There were also mucous patches round the anus and enlarged, hard, and painless buboes in the groin. The skin on the body was the seat of a tolerably confluent erythema, there were adenopathies in the neck and cuneiform pustules on the hairy scalp. The woman had had no treatment. The blood was taken from the cephalic vein in the bend of the right elbow, the skin being previously washed; there were no syphilitic manifestations in this region. All the instruments employed were new. A little pledget of lint was dipped in this blood and then applied to the upper and external regions of the left arm of Dr. Bargioni at the point of the insertion of the deltoid, where the epidermis had been removed and three transverse incisions had been made. The same operation was performed on Drs. Rosi and Passogli, but by that time the blood had already coagulated. The blood-soaked lint was left in place twenty-four hours.

The inoculation was made February 6th, and on March 3d Dr. Bargioni noticed a small rounded papule of a dark red color which itched a little; there was no induration and no swollen glands could be found. A week later the papule was the size of a twenty-centime piece and was covered with a scale. On the 14th there were two enlarged glands, the size of a walnut, in the axilla; they were painless and movable. One week later the scale covering the papule had become a scab, and beneath it was an ulcerated surface with a slightly

indurated base. The following days the ulcer increased in size, its base became frankly indurated, and the neighboring glands became hard, large, and painless. On April 12th there appeared a typical copper-colored erythema accompanied by cervical adenopathy, etc. The syphilis followed its normal course.

This experiment removed all doubt, and it was now shown that a healthy person could acquire syphilis by inoculation with the blood of a syphilitic individual. This does not always happen, but the two following cases are an evidence that it may occur clinically.

The first case occurred in the service of Lorain (Fourchault[29]). On January 12th some fifteen women were revaccinated in the St. Adelaide ward. The physician performed the operation in the manner that was then customary: The heifer was brought into the ward, the vaccine was collected on the blade of a lancet, and the physician carried it to the patients' beds and there vaccinated them in succession, each time dipping the vaccinating needle in the vaccine on the lancet. There was thus a common supply of virus for all those vaccinated. One only of the vaccinated, who was suffering at the time from typhoid fever, contracted syphilis. A month after the vaccination she had a raised ulcer at the site of one of the points of inoculation, and this was followed by a secondary eruption of syphilis, which was benign in its course. The vaccinifer was a heifer and could not be accused of having communicated syphilis, but the disease was carried, from one of the vaccinated having syphilis to another healthy woman, on the point of the vaccinating needle. Lorain has related to me a similar case which he has observed in his own practice. It was that of an old man who was inoculated by the blood of his grandson, twenty-four years old, who had syphilis at the time and who was vaccinated just before his grandfather.

We do not yet know during what stage of syphilis the blood can serve to carry the infection, but it is undoubted that at some period the blood of a syphilitic is capable of producing the disease in another person by means of inoculation. Fournier believes that the blood plays the chief rôle in vaccinal syphilis, but thinks that there is no proof at hand of this belief. I believe that while the possibility of infection through inoculation of blood has been proven experimentally, that of inoculation through the vaccine lymph without admixture of blood has not been proved in this clear manner. I do not deny that vaccine lymph may contain syphilitic virus, but there is no proof of this, and the probability points the other way.

Before animal vaccination had supplanted arm-to-arm vaccination, the question of hereditary syphilis was much discussed and the necessity of its diagnosis insisted upon. We need only remark that

it is impossible absolutely to avoid all error in this respect. Depaul advised that vaccine be taken only from children several months of age in order to allow time for the manifestation of any possible hereditary syphilis. Diday drew up a table based upon one hundred and fifty-eight cases of hereditary syphilis showing the period at which the first symptoms of the disease appeared, as follows:

Under 1 month	86
Between 1 and 2 months	45
" 2 " 3 "	15
" 3 " 4 "	7
" 4 " 5 "	1
" 5 " 6 "	1
" 6 " 8 "	1
" 8 " 12 "	1
" 1 " 2 years	1

Hereditary syphilis, however, reveals itself sometimes much later than this table would lead one to suppose. In any case, even assuming that this is correct, in waiting several months we diminish the chances that the vaccinifer is syphilitic, but we cannot be absolutely certain.

Vaccinal Leprosy.—Gairdner[30] has published a case in which leprosy was communicated by vaccination.

Tuberculosis.—The question of the possibility of the transmission of tuberculosis in vaccination has occupied the attention of many experimenters. Verneuil[31] and Besnier[32] believe that the inoculation of tuberculosis in the course of a vaccination is possible; Chauveau[33] and Bollinger[34] regard it as improbable; Straus[35] has sought in vain for the bacillus of tuberculosis in vaccine lymph taken from subjects who were undoubtedly tuberculous, and Josserand[36] and Straus have introduced serum from vaccine vesicles of tuberculous subjects into the anterior chamber of the eye of rabbits and into the peritoneal cavity of guinea-pigs without any results whatever. The question may therefore be still regarded as *sub judice*, but until it is definitely settled we ought to take all the precautions we would were the possibility an acknowledged fact.

Animal Vaccine.

If we bear in mind the accidents of vaccination which we have just been studying, it will be easy to see what precautions are necessary and sufficient to protect the vaccinated subject from these complications. All that is necessary is to take the virus from heifers which are known to be absolutely free from disease of any sort, to inoculate on a skin which has been made aseptic, and to use instruments which are surgically clean. It is admitted by all authorities

of the present day that animal vaccination is the method which should always be employed, other proper precautions of course not being neglected.

To Troja belongs the credit of first suggesting animal vaccination. Others had, in order to prevent degeneration of the virus or for the sake of scientific experiment, inoculated the udder of the cow with human vaccine, but Troja's object was entirely different. He was director of vaccination in Naples, and as early as 1804 he regularly inoculated heifers with human vaccine in order to insure a supply of virus. He believed also that, vaccina not being a disease proper to the human race, it would be likely to degenerate in the course of its passage through successive generations of men. When Troja left Naples in order to follow the fortunes of the royal family, of whom he was the physician, one of his pupils, Gennaro Galbiati, became director of the vaccine service, and in 1810 he published a memoir[37] of which the following were the titles of two chapters: "1. Vaccination performed with vaccine from the cow manifests its effects much more energetically, without being more dangerous or less protective than humanized virus. 2. Vaccination performed with virus from the cow offers the advantage that no other diseases can be communicated by it." Galbiati affirmed, as the result of his observations, that there is a possibility of transmitting syphilis by arm-to-arm vaccinations.

Galbiati's successor, Negri, continued at first the methods of his predecessors, but later advised direct transmission of the virus from heifer to heifer.

Dr. James, in 1844, in Paris, without citing the Neapolitan practice, of which perhaps he was ignorant, proposed the organization of a service of animal vaccination, and this flourished for some months in the Rue Saint-André-des-Arts. Public opinion was not prepared for this yet, however, especially as the occurrence of cases of vaccinal syphilis was unknown or persistently denied. But when Viennois, in his thesis in 1860 and later in a paper read before the Congress of Lyons in 1864, had shown the frequency and the gravity of cases of vaccinal syphilis, one of the members of the Congress, Dr. Palasciano, recalled the fact that a service of animal vaccination had existed in Naples since 1804. In consequence of this Lanoix and Chambon went to Naples and returned to Paris to found the first vaccinal institute in France. Thanks to these workers and to Saint-Yves Ménard the method of animal vaccination had been transformed. I shall not follow the various steps of its evolution, but will simply describe the method as it is employed to-day in the establishments in Paris, which is practically identical with those in use in other countries.

The chief concern is to obtain on calves an eruption which is perfectly characteristic in its features and regular in its evolution, and then to collect perfectly pure vaccine free from any admixture with pathogenic microbes. In order to secure this it is necessary to work with absolute cleanliness and to maintain perfect asepsis. The barn must be as clean as an operating-room and free from the manure heaps present in barns ordinarily, and every day it must be washed out with an abundance of water, containing if necessary some antiseptic solution. The animal's bed should be of fresh, clean straw or wood-fibre. The calves must be tied in such a way that they cannot lick the vesicles and so rupture them. The inoculation-hall and the laboratory must be established so as to be free from the danger of contamination of any sort.

In many establishments, after the cowpox has been cultivated for several successive generations, reinoculation, retrovaccination is practised; that is to say, heifers are inoculated with humanized vaccine, experience having shown that cowpox degenerates rather rapidly unless it is passed through the human organism. According to Chambon and Saint-Yves Ménard, however, the cause of this degeneration is not the indefinite cultivation on the same soil, but rather the admixture of strange microbes, and they believe therefore that reinoculation is useless.

Calves should be selected which are weaned, those aged from four to six months. Before inoculation they should be kept for some time in a special barn, for having been bought in the open market they might be infected with aphthous fever, pleuropneumonia, or some other disease. Villain, the chief of the service of meat inspection in Paris, affirms that he has never seen a tuberculous calf between the ages of four and six months among the 753,851 calves of this age killed in the abattoir during the years 1888–89-90, so that the danger of the transmission of tuberculosis under these conditions would seem to be excluded.

Before being inoculated the animals should be most carefully cleaned with the currycomb, soap and water, and disinfectant solutions. At first inoculations were made only in the mammary region, but Chambon soon extended the field of inoculation to the entire thoracoabdominal surface. We may in this way obtain from one hundred to one hundred and twenty vesicles, the virus being no more weakened by the multiplicity of vesicles than is that of confluent smallpox because the pustules are numerous. The field of inoculation is shaved and washed with a three-per-cent. boric-acid solution or a solution of sublimate, 1 : 2,000. The inoculation is made by punctures, incisions, or scarifications, and a drop of vaccine is placed

at this point; incision appears to be preferable, for it gives rise to a larger vesicle and consequently to a greater amount of lymph.

The following is the description of Chambon and Saint-Yves Ménard of the evolution of cowpox when inoculation has been practised by means of an incision: "The first, second, and third days after that of the inoculation are days of incubation, during which the wounds cicatrize more or less completely but without any objective symptoms. The healing is so perfect that we may be led to doubt whether the vaccination has been effectual or not. If any redness or swelling appears at this time we regard it as a sign of impurity of the vaccine. On the fourth day, however, the appearance of a slight redness and of a moderate swelling is a normal occurrence, and the line of the original incision is now bordered by two white lines. On the fifth day these lines become a silvery gray zone formed by an elevation of the epidermis and limited by a red border. The pustule is very distinctly marked off and it presents a longitudinal depression corresponding to the original incision. On the sixth day the size of the lesion is increased and the white border is enlarged and tense. On the seventh day the pustule has reached its maximum of development, and this is the last day that the heifers can be utilized as vaccinifers. The following days the pustules become flattened, their surface becomes wrinkled and dried and is transformed into a scab, at first yellowish and then blackish; this is detached on the sixteenth or seventeenth day, leaving an oval cicatrix. When the inoculation has been well done the development of the pustules is uniform throughout the entire vaccinal field. The evolution of the vaccine is not accompanied by any appreciable general reaction, but, on the other hand, there is always a very marked swelling of a subcutaneous lymphatic gland above and behind the field of vaccination."

Unfortunately it happens quite often even in the best-regulated vaccine establishments that the eruption becomes modified and the virus loses some of its strength. In order to avoid what has been called the "purulence" of the vaccine many procedures have been recommended. Chambon and Saint-Yves Ménard, in a series of experiments made in collaboration with Straus in 1889–90, found that lymph taken from slightly abnormal lesions did not contain, as Pourquier, of Montpellier, thought, a "parasite of cowpox," but rather a large collection of strange microbes. They believed that these microbes increased in number with each generation and finally overpowered the as yet unknown organism in which resides the specific virulence of the vaccine. Following up their experiments, these observers discovered what they regarded as a certain means of securing a lymph completely free from any foreign microbes and capable of

invariably reproducing a most pure vaccine. They remarked that when the seed vaccine had by chance been kept four or five weeks it seemed to produce a more beautiful eruption, and pursuing their investigations they found that the glycerinized pulp which, when used fresh gave indifferent results, would produce a fair lesion if used at the end of two weeks, and a typical eruption when kept for forty, fifty, or sixty days. They believed that this improvement was due to the gradual destruction of the parasitic microbes through the action of the glycerin and of time, and Straus proved the truth of this explanation by means of plate cultures of the glycerinized lymph at different ages. The sowing of the fresh pulp gave numerous colonies of microbes of various kinds, among which were found the staphylococcus pyogenes aureus and the staphylococcus albus, while sowing of the glycerinized pulp fifty or sixy days old showed that it was absolutely sterile, intermediate specimens giving fewer and fewer colonies in direct proportion as they were older.

I need not enter here into the details of the processes employed in the collection of the vaccine, for the technique of this concerns only the directors of vaccine establishments. I may say, however, that there has been an enormous progress made in the preparation of animal vaccine and that its preservation is now assured by the addition of glycerin. The effect of the glycerin is to prevent putrefaction of the organic matters contained in the vaccinal lymph and to preserve the vitality of the specific principle of the virus. The prepared lymph is enclosed in tubes 1 mm. to 1.5 mm. in diameter, the ends of which are sealed in the flame. Well-prepared glycerinized vaccine pulp preserves its activity over a year (Deschamps[38]), especially if care be taken to keep the tubes at a temperature below 15° C. (59° F.).

Indications and Contraindications of Vaccination.

From what has been said we see that it is possible now to employ an absolutely pure animal vaccine, so that there need be no danger whatever of transmitting any disease such as syphilis, septicæmia, or the like. As the bovidæ are very subject to tuberculosis we may yet fear the inoculation of this disease, but Straus has shown how improbable this is, and Villain's statistics have demonstrated the fact that tuberculosis is very rare in calves between the ages of four and six months. We may, however, go still further, and obtain an absolute security. The animals which have served as vaccinifers might be immediately slaughtered, the vaccine obtained from them being kept several months and not employed until an examination of

the slaughtered animals had shown that there was no trace of tuberculous trouble in any of the organs.

We may then be absolutely sure that the vaccine furnished by the animal is pure, and elementary antiseptic measures will insure that no foreign and pathogenic organism can enter during or subsequent to the slight operation. Whatever instrument is employed it should be made aseptic by passing through a flame each time before being used to vaccinate another person. Always, except in case of great emergency, animal vaccination should be employed in preference to the arm-to-arm method.

Age, sex, and season may be invoked in special cases as contraindications to vaccination, but in maternities the children are vaccinated a few days after their birth, whatever the season of the year, and no trouble has ever resulted from this practice.

With the exception of certain skin affections in which the danger of autoinoculation may exist, intercurrent diseases offer no contraindication to vaccination. According to Trousseau a preëxisting scarlatina will arrest the development of the vaccina until the primary disease is over, and then the effects of the vaccination pursue their regular course.

Vaccination during the incubative period of smallpox exerts no injurious effect, but on the contrary seems sometimes to influence favorably the course of the disease. The physician ought therefore to pay no attention to the popular prejudice which would forbid vaccination during an epidemic of variola.

When a child has a nævus it has been advised to vaccinate on it, the number of insertions corresponding to the size of the tumor, as the cicatrization of the pock causes a contraction of the blood-vessels and sometimes leads to the disappearance of the vascular growth.

Methods of Vaccination.

After having made the field of operation aseptic we must look to the absolute surgical cleanliness of the instrument to be employed. It is of little consequence whether we use a lancet, a needle, or the metallic pen called the vaccinostyle; but we must cause the vaccine to penetrate beneath the epidermis, must avoid causing the little wound to bleed, and must see that the wound is not contaminated after the vaccination. Whether we employ incisions or scarification we should not make the insertions too close together, separating them by about an inch.

The custom is to make the inoculation on the arm at about the point of insertion of the deltoid. Some mothers, in order to avoid a

disfiguring scar on the arm, ask to have their daughters vaccinated on the thigh or calf of the leg, and ordinarily this wish may be respected without any harm. We should remember, however, that there is some danger in the case of an infant that the vaccination wound may be soiled by urine or fæces, and we therefore should be very careful to cover the points of inoculation with a good dressing and to impress upon the mother the necessity of seeing that this dressing be not disturbed.

Of late years vaccination by scarification has been strongly recommended, but I do not believe that it is any better than the old method of incision. If the new method be used, however, care should be taken that the lines of scarification should not exceed 2 or 3 mm. in length; an objection to them is that they demand a greater manual dexterity than does the old practice of insertion of the virus through a minute incision or puncture.

Bibliographical References.

1. Jenner: Complete Works., London, 1801.
2. Bouley: Bulletin de l'Académie de Médecine, June 30, 1863.
3. Depaul: Bulletin de l'Académie de Médecine, December 1, 1863.
4. Surmont: Article "Vaccine," Traité de Médecine et de Thérapeutique, edited by Brouardel, Gilbert, and Girode, vol. i., 1895, p. 192.
5. Juhel-Renoy: Comptes rendus de la Société de Médecine des Hôpitaux de Paris, 1893.
6. Dupuy: Thèse de Paris, 1894.
7. Straus, Chambon et Saint-Yves Ménard: Comptes rendus de l'Académie des Sciences, cxi., 1890, p. 978.
8. Layet: Traité de la Vaccination animale, Paris, 1889.
9. v. Jaksch: Jahrbuch für Kinderheilkunde, vol. xxviii., Nos. 3 and 4.
10. Erich Peiper: Ueber das Vaccinfieber. Zeitschrift für klinische Medicin, 1 and 2, 1890.
11. Sobotka: Zeitschrift für Heilkunde, No. 5, 1893, p. 329.
12. L. Perl: Berliner klinische Wochenschrift, No. 28, 1893, p. 674.
13. D'Espine: Article "Vaccine," Dictionnaire de Médecine et de Chirurgie pratiques, 1885.
14. Sacco: Trattato di Vaccinazione, Milan, 1809.
15. Maurice Raynaud: Comptes rendus de l'Académie des Sciences, 1877, p. 454.
16. Lalagarde: Études sur la Vaccination, Paris, 1856.
17. Saint-Yves Ménard: De la Vaccine et de la Vaccination. La Médecine Moderne, 1891.
18. Raths: Arbeiten aus dem kaiserlichen Gesundheitsamte, vi., 1, p. 100.
19. Cadet de Gassicourt: Bulletin de l'Académie de Médecine, 1893, p. 371.
20. Jeanselme: De la Vaccine généralisée. Gazette des Hôpitaux, 1892, p. 253.
21. Ausset: Rapport général sur la Vaccination, Académie de Médecine, 1894.
22. Pincus: Die Impfung in Grabnick. Vierteljahresschrift für gerichtliche Medicin, etc., July, 1879.

23. Hervieux: Vaccine ulcéreuse. Bulletin de l'Académie de Médecine, September 18 and November 26, 1889.

24. Leloir: L'Épidémie de Vaccine chancriforme de la Motte-aux-Bois. Bulletin Médical, 1889, p. 1,419.

25. Viennois: Transmission de la Syphilis par la Vaccination. Archives Générales de Médecine, June, 1860.

26. Depaul: De la Syphilis vaccinal à l'Académie de Médecine, Paris, J. B. Baillière, 1865.

27. ———: Gazette des Hôpitaux, 1867, p. 418.

28. Pellizari: Gazette Médicale de Lyon.

29. Fourchault: Thèse de Paris, 1866.

30. Gairdner: British Medical Journal, June 11, 1887.

31. Verneuil: Bulletin de l'Académie de Médecine, January 22, 1884.

32. Besnier: Annales de Dermatologie et de Syphiligraphie, 1889, p. 576.

33. Chauveau: Gazette hebdomadaire, 1872, p. 249.

34. Bollinger: Zur Aetiologie der Tuberculose, Munich, 1883.

35. Straus: La tuberculose est elle transmissible par le vaccin? Société médicale des Hôpitaux, February 13, 1885.

36. Josserand: Contribution à l'étude des contaminations vaccinales, Société médicale des Hôpitaux, February 13, 1885.

37. Gennaro Galbiati: Memoria sulla inoculazione coll'umore ricavato immediatamente dalla vacca precedentemente inoculata, Naples, 1810.

38. Deschamps: Revue d'Hygiène et de Police Sanitaire, April 20, 1892.

MUMPS.

BY

JULES COMBY,

PARIS.

MUMPS.

We may define mumps as an infectious, contagious, epidemic disease, attacking by preference young subjects, localized in the salivary glands, especially the parotid, but affecting the entire economy after the manner of the general diseases.

Mumps, called in French *oreillons, ourles, fièvre ourlienne, parotide épidémique*, has also been designated at various times parotis, parotitis, parotiditis, cynanche parotidea, angina maxillaris, angina externa, a diversity of appellations which has no other value than as witnessing to the confusion which has long reigned in medical nosology.

History.

Mumps is a disease of very ancient lineage, our knowledge of it going back to the farthest medical antiquity, as witness the very clear description given of it in the works of Hippocrates[1]: "*Swellings* appeared behind the ears, in many on one side, in most on both, without a Fever or any confinement, but in some with a little Fever. In all they disappear'd without either inconvenience or suppuration, contrary to the custom of such tumors from other causes. At this particular time they were naturally soft, large, diffus'd, without inflammation or pain, and went off universally without any visible signs. Children, young persons, adults, especially those who frequented the public places of exercise, were most subject to them. A few women were also affected. The greatest part had *dry Coughs*, which were soon succeeded by *Hoarsenesses*. Some again after a while had *painful Phlegmons upon the Testicles*, sometimes upon one, sometimes upon both. Some had fevers, others none; most of 'em trouble and fatigue enough: but with respect to the *chirurgical* part they did very well."

After the time of Hippocrates, however, the clinical knowledge of mumps was lost for ages. Our great surgeon, Ambroise Paré, did not distinguish cases of mumps from those of secondary parotiditis, and even confounded them with adenopathies in neighboring regions. "Parotiditis," he wrote, "is an unnatural swelling involving the glands and neighboring parts which are below the ears." The same confusion is noted in the writings of Sennert, Van Swieten, J. Ca-

puron, and others. Every periauricular swelling was called parotis: "Est enim parotis glandularum juxta aures inflammatio." J. Capuron errs even more widely from the truth: "We give," he says, "the name of oreillons to the swelling of the parotid glands. Tumors of this sort are almost always produced by the process of dentition, or by a sudden drying up of ulcerated or suppurating ears; they depend also sometimes upon a scrofulous vice; they are accompanied or not by fever according as there is a simple swelling or an inflammation of the glands." This quotation shows that the notion of mumps held by physicians of the first quarter of this century was a very confused one. The Hippocratic description was a dead letter so far as concerned most of the physicians of this epoch. Nevertheless some physicians, even in the preceding century, had felt and expressed a part of the truth in the presence of epidemics of mumps. Hamilton (epidemic in Scotland in 1761) had a quite correct idea of the disease and noted the occurrence of orchitis and of testicular atrophy as sequelæ of mumps. Mangor (epidemic of Wiborg in 1773) asserted that the affection was contagious. Numerous epidemics observed in Italy in the course of the eighteenth century established this question of contagiousness beyond doubt, and the accounts left us by Gaspari (Istria, 1714), Targioni Tozzetti (Florence, 1752), and Laghi (Bologna, 1753) did much to elucidate the question of contagious and epidemic parotitis.

J. Pratolongo, who had studied an epidemic of mumps in Genoa, wrote to Borsieri in 1752 as follows: "The only disease which we can regard as epidemic in Genoa at present is that which we call mumps. In addition to the swelling of the parotids we have seen in some patients an enlargement of the testicles together with a violent fever. In others this swelling of the parotids was followed by an anasarca such as sometimes supervenes upon an attack of scarlatina, accompanied by great difficulty in breathing and a sharp fever. Do you think that we could class this disease among the eruptive fevers?"

This opinion was adopted by Trousseau, Colin, Laveran, and all who, seeing much of mumps, were not slow in recognizing the specific nature of the disease. I have dwelt at length on this point in a recently published monograph,[2] and we may say that to-day there is but one opinion concerning the nature of mumps.

Geographical Distribution and Epidemics.

Parotitis occurs at all seasons and in all countries. It was once thought that mumps did not occur in the tropics, but this was only because the disease lacked an historian in these regions, for it is

found everywhere. Contagion is the sole factor in the distribution of the malady, climatic influences counting for nothing in this respect. Introduce mumps into a regiment, and whether this regiment be in garrison in London, Malta, Calcutta, or Singapore, the propagation of the malady will be precisely the same, and the number of victims will be influenced in not the slightest degree by the temperature.

This is not a theoretical statement merely, for proofs exist in abundance. Laveran says that mumps is as common in Algeria as in France, if we may judge by the medical statistics of the French army. During the four years 1862–65 the number of patients admitted to hospital for treatment for mumps was for the garrisons in France 367, for those in Algeria 122, and for those in Italy 7. "The effective of the troops in France for this period being five or six times that of the troops in Algeria, we see that mumps occurred with as great frequency in Algeria as in France." These figures also, adds Laveran, give but a faint idea of the frequency of mumps in the army, since they refer only to those patients who were treated in the hospital, but most of the men suffering from mumps are treated in the infirmaries. During a period of eleven years from 1862 to 1874 (the years 1870 and 1871 being excepted) we find but one death due to mumps in the army in Algeria.

Thierry de Maugras reports 74 cases of mumps during an epidemic which attacked a column 1,200 strong returning to Mascara, and Widal saw 33 cases among the members of the 87th regiment at Milianah, one-half of the cases being complicated with orchitis.

Leaving Africa, we find the disease prevailing in emigrant ships in India. Dangaix in two voyages from the East to the West Indies reported 88 and 147 cases respectively occurring on the vessel a week after departure. Huiller has noted the frequency of mumps at Pondicherry. Jobard relates the history of two epidemics occurring among the Indian emigrants on board the *Contest* (83 cases among 471 passengers) and the *Medusa* (67 cases among 512 passengers). On the first of these vessels the epidemic declared itself five days and on the other twenty-three days after sailing from Karikal.

The disease prevails no less in the United States, and the statistics of the Civil War show us that parotitis is as common there as in Europe. During the first year of the war there were 11,216 cases with 9 deaths, in the second year 13,429 cases with 30 deaths. This relatively high mortality leads Laveran to question the statistics, and I am inclined to agree with him in thinking that cases of parotitis of another nature were included in these figures.

Parotitis usually occurs in small epidemics which are circum-

scribed to rather limited areas, collections of young people, as those in schools and garrisons, feeding such epidemics for the most part. The disease accidentally introduced into such a favorable locality quickly spreads, but it often spends its force in one place without spreading outside. The power of expansion of mumps is therefore not comparable to that of measles, variola, whooping-cough, or influenza. The contagiousness of the malady is undeniable but it is restricted, as we may see clearly by a study of epidemics of the disease. Thus we have histories of very many epidemics in which the disease was limited wholly to single schools, orphan asylums, or garrisons. Sometimes the mumps remains confined to one regiment, sometimes it spreads to the other troops in garrison while not attacking the civilians of the place, although it may extend to the town outside of the garrison.

In exceptional instances the disease may extend far and wide, Laveran having reported cases in which mumps spread throughout entire provinces. In 1714 an epidemic of mumps extended throughout Istria; in 1753 it invaded Bologna, Ferrara, Mantua, the Marches, and Rome; in 1782 Northern Italy (Milan, Turin, Genoa) was attacked; in 1786–87 Trevise, Vicenza, Verona, Venice, and Padua; in 1826 Saxony; in 1829 the canton of Zurich; in 1835 Treves and Düsseldorf; in 1841 Cologne and its environs; in 1851 and 1856 Sweden. In an epidemic which prevailed in Geneva in 1848–49 the neighboring cantons were invaded.

It has been stated that mumps occurs more frequently in winter than in summer. Out of 117 epidemics Hirsch found 51 occurring in winter, 32 in the spring, 15 in summer, and 19 in the autumn.

Pathological Anatomy.

Mumps is not a fatal affection, and consequently the occasions of studying the lesions of the disease are very rare. Virchow believes that in mumps there is an inflammation, ordinarily catarrhal and seldom suppurative, of the ducts of the parotid glands. On the other hand Trousseau and Cadet de Gassicourt assert that the lesions do not proceed beyond hyperæmia and congestion, and they distinguish sharply between epidemic mumps and the parotiditis secondary to infectious diseases.

In the case of a soldier who died of œdema of the glottis during an attack of mumps, Jacob found the following lesions: The actual substance of the parotid and submaxillary glands was not increased in size, but their cellular atmosphere was filled with a greenish, transparent, gelatinous fluid which gave to the tissues a lardaceous

consistence. A microscopical examination made by Ranvier showed neither inflammation of the glands nor lesion of the neighboring lymphatic ganglia. The epithelium of the salivary ducts was intact, there was no cellular proliferation, and the interacinous connective tissue was not œdematous. The œdema was glottic and periparotidean solely. In simple cases, then, there is no inflammation of the parotid gland, but there doubtless is in cases complicated with suppuration. Here, however, there is a secondary infection added to the parotid trouble.

The lesions of the testicles, which are so often affected in mumps, have been made the object of special study. Reclus found the testicle soft, flaccid, and atrophied. The tunica albuginea, too large for the shrunken gland, was wrinkled, and the substance of the testicle itself was bloodless, opaline, and of a milky whiteness. On section the surface was smooth, the seminiferous tubules were faintly marked, and although they could still be unrolled they were very soft and quickly broke. The histological examination, made by Malassez, showed that the intercanalicular connective tissue was not thickened, and the vessels were healthy; the seminiferous tubules were diminished in volume (60 to 120 μ, instead of 150 to 200 μ); the outer coat of the tubes was unchanged but the inner tunic was thickened, the epithelium was gone and the tubes were converted into simple cords. According to Reclus the lesion was a parenchymatous sclerosis of the testicle.

Quinquaud has made a chemical study of the blood. He found that the hæmoglobin was but little altered, being normal in amount or perhaps reduced to 110 per 1,000; the albumin was diminished in amount possibly even as far as to 65 gm. per 1,000 or lower; the fibrin to from 3 to 5 gm.; while the products of disassimilation were increased to 8, 12, or 14 gm. There was but little increase in the proportion of urea.

Griffiths has found a ptomaïn in the urine which, when injected into a cat, caused death after convulsions and the suppression of the salivary secretion.

Bacteriology.

Since parotitis presents all the appearances characteristic of an infectious disease, it is very natural that search should have been made in the bodies of those suffering from the disease for a specific microorganism. As early as 1881, in a communication made to the Biological Society of Paris, Capitan and Charrin announced the discovery of certain microbes in six pupils of the Polytechnic School who were suffering from mumps. These microbes, found in the

blood and occasionally in the saliva, were for the most part spherical, sometimes in the shape of elongated mobile rods. "There was never anything in the urine and seldom any distinct forms in the saliva, but the blood contained a very large number of microbes, most abundant during the height of the disease and diminishing gradually as convalescence supervened, but becoming very markedly less numerous in those cases in which orchitis occurred." These microbes had variable forms, rods 2 μ in length by $\frac{1}{2}$ μ in thickness, and micrococci, single, double, or in chains. Cultures were made, but inoculations in dogs, rabbits, and guinea-pigs gave negative results.

In a case reported by Karth,[3] Bouchard found bacteria in the saliva from Steno's duct, and also in the urine which contained albumin. Later Ollivier[4] confirmed the researches of Capitan and Charrin. In the case of a boy, eleven years old, an examination of the saliva showed bacilli and micrococci in the midst of epithelial cells and leucocytes. These micrococci, single or united in twos and fours or in zoöglœa masses, were not more than $\frac{1}{2}$ μ in diameter. They were found also in the urine. Nothing similar was found in two other children who were not suffering with mumps. In two other children affected with mumps the saliva, blood, and urine contained micrococci, diplococci, and short and mobile bacteria. These elements disappeared after recovery. Boinet found similar micrococci in fifteen patients with mumps. Bordas, on the other hand, found no micrococci in the blood, but a bacillus (bacillus parotidis) which was sometimes enlarged at each extremity, and occasionally assumed the form of an S or a V before division. When the culture medium was poor there was a spore formation. The bacillus was quite resistant at ordinary temperatures, but succumbed at 60° C. (140° F.), the spores resisting up to 90° C. (194° F.). Sublimate and boric acid destroyed the bacillus, but iodoform did not. Bordas believes that the saliva is the true vehicle of contagion, and that the disease develops only after the deposit of spores in Steno's duct.

The more recent researches of Laveran and Catrin have advanced greatly our knowledge concerning the bacteriology of mumps. These investigations and their results are thus described by Catrin[5]: "In 1892, in my service of contagious diseases at Val-de-Grâce there came a large number of cases of mumps, and Laveran and myself thought it would be opportune to study these cases bacteriologically. We examined not only the blood but also the serous fluid from the parotid gland and the neighboring parts, from the testicle, and from the œdema in certain parts, and also the articular fluid in certain cases of rheumatism complicating mumps. These researches were of the most simple character, and our results have since been confirmed by

others in the case of adults. The puncture of the organs or cellular tissue was made by means of a fine needle fitted to a hypodermic syringe. Antiseptic precautions were employed, and no accident was caused by the simple operation; indeed, the puncture in certain cases seemed to have a beneficial therapeutic effect, especially by way of relieving the pain in cases of testicular complications.

"Of ninety-five cases which formed the basis of our studies, we obtained positive results in sixty-seven. In thirty-nine out of fifty-six times we obtained pure cultures by puncture of the parotid glands, twice the cultures were impure, and fifteen times no result was obtained. These negative results may be explained by the occasional absence of any fluid in the organ, so that the plates were sown merely with the sterilized water contained in the needle. In most cases the amount of fluid extracted did not exceed a few drops.

"The testicular fluid, on the other hand, almost constantly gave positive results, that is to say, twelve out of sixteen experiments; the fluid removed from points of localized œdema gave a positive result in all the cases examined (three), and the same is true in the two cases in which fluid from a swollen knee-joint was examined.

"In ten out of fifteen examinations of the blood while fever was present the same microorganisms were found as in the fluid removed from the various organs. We found the microbe two and even three weeks after apparent recovery from mumps, a fact which serves to explain the rare instances of contagion during convalescence. After a month had elapsed our researches were always negative in their results.

"In the pus of an abscess of the neck which formed in one of our cases, we found a pure culture of staphylococcus pyogenes aureus which resembles in no way the microbe discovered by us in the parotid glands.

"The organisms found by us were micrococci, usually arranged in pairs, sometimes in fours, and rarely in zoöglœa masses. These cocci measured from one to one and a half micromillimetres in diameter; they were mobile but not markedly so. They were colored readily with the ordinary stains, but unlike streptococci and staphylococci they did not receive Gram's staining. The bouillon, kept in an oven at 35°, showed changes at the end of from twenty to twenty-four hours, and these increased markedly later. Colonies on gelatin plates did not appear until the expiration of forty-eight hours; they were punctiform, white in color, grew slowly, and liquefied also very slowly and tardily. In stab cultures the colonies developed as very minute pearls along the track of the puncture; liquefaction began at the surface and proceeded very slowly. On potato the whit-

ish culture was scarcely apparent, but it was more so on carrot. The whitish culture on serum presented no peculiarities.

"We could not expect very convincing inoculation experiments, since no known animal except the horse (?) is susceptible to mumps. Subcutaneous, interperitoneal, and intravenous injections gave only negative results in guinea-pigs and rabbits. Injections into the connective tissue caused no reaction, but those into the testicle excited a very acute orchitis of short duration, ending in recovery by the end of a week. These last experiments were made in rabbits and dogs, but we were unable to follow up the animals long enough to see whether testicular atrophy supervened. In white mice four out of twenty-six inoculations were followed by death, and on examination the spleen was found enlarged. Four of these inoculations were made into the peritoneum, and in three of these death occurred, the peritoneum showing evidences of inflammation. In all the fatal cases the diplococcus above described was found in the blood removed from the heart cavity with all the usual precautions."

These researches of Laveran and Catrin have been confirmed by other investigators. Busquet and Ferré[6] found a similar diplococcus in seventeen cases in the blood taken from the pulp of the finger and the lobe of the ear, and in the fluid from the parotid gland. In the saliva removed by a pipette from Steno's duct they found a diplostreptococcus either alone or in company with the diplococcus found elsewhere.

P. M. Mecray and J. J. Walsh[7] found the same diplococcus in cultures made from the contents of Steno's duct during the height of the disease. They claim to have isolated and cultivated this diplococcus before having learned of the work of Laveran and Catrin. The following was their method of procedure: The mouth having been carefully cleansed with a saturated solution of boric acid, the orifice of Steno's duct, after this had been emptied by light massage of the cheek, was covered for a period of five minutes with a piece of cotton wet in the same solution. A bit of sterile silkworm gut was then introduced into the duct and from it an agar slant was inoculated. "Out of ten tubes six had a mixed growth, but in all of them there was noted a small, white, slow-growing colony. This was isolated in plate cultures and was found to contain two different organisms, one a streptococcus form, the other a micrococcus, nearly always seen as a diplococcus. Further culture showed that the streptococcus grew more rapidly and liquefied gelatin sooner (in three to five days) than the micrococcus. It did not occur in the original cultures as constantly as the latter, the diplococcus form, occurring for certain in eight of the ten tubes and being considered

to be present in the others, though this could not be demonstrated with certainty, owing to invasion of the colonies by the more rapidly growing cocci so common in the mouth, which our precautions had not succeeded in entirely eliminating." The blood was examined in eight cases. "Out of the eight tubes two gave an entirely negative result, three gave pure cultures of the characteristic diplococcus, and three gave a mixed result, the diplococci being found, but with them other cocci, notably a staphylococcus form, probably the staphylococcus epidermidis albus. Control tests made from the blood of five healthy children gave absolutely negative results. Cultures made from Steno's duct in these same children gave us various oral microorganisms in four cases, but not the diplococcus found in the mumps cases." The experiments were not carried any further, no animal inoculations being made.

Michaelis[8] obtained analogous results. He found in Steno's duct diplococci in chains and resembling somewhat the gonococcus or the meningococcus. These were also found once in the blood. Inoculations in animals gave negative results.

Notwithstanding these interesting observations we cannot say that the demonstration is complete. The experimental proof is wanting, that is to say, the reproduction of the disease in animals by inoculation with cultures of this microbe. There yet remains to be done for mumps what Pasteur has done for anthrax and chicken cholera, what Villemin and Koch have done for tuberculosis, and what Bouchard, Capitan, and Charrin have done for glanders. For the present we must content ourselves with recording the facts simply. Microbes have been found present in cases of mumps, and these microbes have been cultivated; but in order to demonstrate that these microbes are really the exciting cause of mumps we must reproduce the typical picture of the disease in an animal by means of cultures of this microbe.

Etiology.

The facts which we have already discussed permit us to foretell the mode of propagation of mumps. The sole cause of the disease is contagion, but we may review briefly the multiple and diverse conditions under which contagion becomes effective.

The disease occurs for the most part in the form of epidemics of greater or less extent, and the frequency of its occurrence is dependent entirely upon the presence or absence of these epidemics. Thus a city may have in one year hundreds or thousands of cases of mumps, and during the following or several successive years there may not be a single case. The disease is very common in the army

in regiments in garrison, and wherever there are large aggregations of young men. In the French army from 1888 to 1892 there were 33,745 cases of mumps. The disease is very common in schools, but rarely attacks nursing children.

As regards age, Rilliet and Lombard found out of 73 patients with mumps, none under 2 years of age, 7 from 3 to 5 years, 18 from 5 to 10 years, 19 from 10 to 15, 8 from 15 to 20, 9 from 20 to 30, 8 from 30 to 40, 2 from 40 to 50, 1 from 50 to 60, and 1 from 60 to 70. Thus we see that more than half of the cases were observed between the ages of 5 and 15 years; after 50 years there were but two cases, and before the end of the second year there was none. V. Gautier, however, has reported a case of mumps in a new-born child whose mother had been attacked with the disease at the time of her confinement. In this case the swelling, which was confined to the submaxillary glands, appeared twelve days after the mother had contracted parotitis. A woman, forty-five years old, was attacked with mumps during the eighth month of pregnancy and was delivered before term of a child who had a swelling in the left parotid region. This swelling increased for two days and then disappeared. Adults, although less susceptible than young subjects, may suffer nevertheless. A man, fifty years of age, entered my service in the Hôpital Tenon on April 13th, 1892, suffering from a right hemiplegia with aphasia. Two weeks after admission there appeared a parotid swelling, first on the right side and then on the left. There was no case of mumps in the ward, and on inquiry I learned that this man had been in the same house with a girl six years old, who was suffering from mumps, eight or ten days before his stroke of apoplexy. The study of epidemics in armies shows us that young soldiers are more liable to suffer than are the veterans. This fact has been noted by Cornac, Colin, and Galland in their accounts of various epidemics. Bussard, in a study of 28 cases, found 16 patients who had seen less than one year of service, and 5 who had been between one and two years in the army.

It has been repeatedly affirmed that mumps attacks boys with much greater frequency than girls. This impression has been based on the statements of those who have studied epidemics in boys' schools and colleges, but if we leave aside statistics so gleaned we shall see that this is an error. In the 73 cases above referred to, which were analyzed by Rilliet at Geneva, 38 were in male and 35 in female subjects. In an epidemic observed at Vire by Lepecq la Clôture, children and women were chiefly attacked to the almost entire exclusion of men. Thus we see that sex has no part in the etiology of mumps.

The fact of contagion is evident and is clearly shown in all epidemics as well as by cases occurring in hospital wards. Catrin, in Val-de-Grâce, saw five cases originating within the hospital. In 1887 at Tarascon, all the orderlies in the army hospital were attacked. Cadet de Gassicourt saw a patient in the hospital attacked twenty days after a child suffering from mumps had been placed in the next bed to him. Roth [9] cites cases of contagion travelling from bed to bed and also of contagion carried by the physician. In one case a woman who slept in a bed which had been occupied twenty-two days before by a patient with mumps came down with the same disease. This would seem to show that the pathogenic microbe possesses considerable vitality.

The contagion of mumps is, however, less marked than that of measles. It requires direct contact ordinarily, and instances have been observed in which epidemics were limited by the interposition of a wall, a glass partition, etc. It appears, therefore, that the contagious element is not volatile and cannot be transported to a distance by the atmosphere. During the winter of 1874–75 the disease was epidemic at Oléron. The garrison (two hundred and fifty men quartered in the right wing of the castle of Oléron) was attacked in the month of January. The first case was in a soldier who had passed several hours two weeks before in a room where there were two children sick with mumps. Following this four of the man's roommates were attacked, and later other men up to a total of twenty-eight, of whom sixteen had had less than one year of service. In the left wing of the castle two hundred and twenty sailors were undergoing confinement for various offences, and were therefore strictly isolated, having no intercourse with either soldiers or civilians; none of these had mumps.

In an infant school in Paris there were twenty-five children suffering from mumps. This school was located on the ground floor of a large building the upper stories of which were occupied by a girls' school, having more than two hundred pupils. A wall about eight feet high, pierced by a glass door, separated the playgrounds of these two schools. The glass door was opened only two or three times a day, as required by the necessities of the domestic service, and was at all other times kept tightly closed. This slender and incomplete partition sufficed to confine the epidemic to its place of origin and to prevent it from gaining entrance into the girls' school. In the class room of this infant school, which had an attendance of from one hundred to one hundred and thirty children, according to the time of year, all the pupils were seated on a sloping platform; the benches were eight in number and only 5 metres in length, so

that each child had a space of only about 30 cm. (one foot) in which to sit, and contact of one child with the other was inevitable. Such close and constant contact furnishes a very evident danger as regards the transmission of contagious disease, as witness the progress of the epidemic in this school. On February 11th, 12th, and 13th, there was one case each day; on the 14th, two cases; on the 15th, four; on the 23d, two; on the 27th, one; and on the 28th, three—giving a total of fifteen cases, after which the school was closed. During the eighteen days that this epidemic lasted the pupils in the girls' school, immediately contiguous, remained free. One girl of this school did have an attack of mumps, it is true, but she was in the habit of calling for her little brother every evening at the infant school and taking him home.

Let us see when the disease becomes contagious and how long this period of contagiousness lasts. Rendu has demonstrated by careful observations that the disease is especially contagious at the beginning, even before the swelling of the parotid gland has appeared. Other facts show that the contagion is still active during the height of the disease and even during convalescence. A case in proof of this is reported by Séta.[10] Three children in one family under the care of Dr. Bernutz were successively attacked with mumps. The parents were warned that the disease was contagious and isolation of the patients was recommended. At the end of six weeks the parents asked whether their children could now safely visit their uncle's family in the country. Permission being given, they went there and communicated the disease to their two little cousins.

The contagiousness of mumps was denied in the last century by Béhier, who thought the disease was caused solely by cold, by Vogel, and by others; but it was also positively affirmed by Hamilton, of Edinburgh, in 1759, and by Mangor in 1771. The latter, who saw many cases during the epidemic at Wiborg, says: "Contagium salutavi, nam aliter genealogiam ejus de domo in domum et de homine in hominem explicare nequeo." Following these authors, Ozanam, Cullen, A. Cooper, Bretonneau (who himself contracted the disease from sleeping in the room with a young man suffering from mumps), Trousseau, Rilliet and Lombard, and all military surgeons and pediatric physicians have affirmed the contagiousness of mumps.

It has even been claimed that the disease could be propagated to animals by means of contagion, although inoculation experiments with cultures of the supposed microbe and with fluid matters taken from the bodies of the sick have always given negative results. Busquet[11] asserts that he has seen a dog with parotitis, acquired apparently from his master who was suffering at the time with mumps.

The fluid drooling from this dog's mouth and also the saliva taken from Steno's duct contained diplostreptococci similar to those described by Laveran and Catrin.

We may ask through what channel the pathogenic microbe of mumps enters the organism. It is not at all probable that this is through the respiratory passages, for the bronchi and the lungs are very seldom affected in cases of mumps. The early localization of the disease in the salivary glands speaks in favor of an entrance through the mouth or possibly through the nose by way of the pharynx. It is probable that the microbe becomes mixed with the saliva and passes up through Steno's duct into the parotid gland. This is the opinion of Henoch and of many other writers. But this explanation does not fit well those cases in which the parotid symptoms are delayed and the first manifestation is an orchitis.

Relapses are uncommon in mumps and one attack usually confers immunity for a lifetime. Rilliet insists especially upon this immunity, and says that he has observed some very conclusive facts in this direction. "Thus I have seen a father and his children contract the disease, while the mother escaped in consequence of having had mumps previously in Paris. I have remarked the same thing in the case of a child eight years of age who had had the disease two years before, and who in this epidemic was the only one of his family who escaped. Finally I have satisfied myself by inquiries that those who have had mumps this year never suffered from the disease before." There are, however, exceptions to this rule, and as medical literature becomes more voluminous the reported cases of relapse become more and more numerous. Servier has seen a soldier who suffered from mumps, although he had had the disease five years before and had an almost complete atrophy of one testicle in consequence. Jacob saw two cases of relapse in the same epidemic. Nimier reports the case of a man who had four attacks of mumps in three years, and cites two other instances of recurrence after an interval of one year. Antony has seen three similar cases, Nicholson one recurrence after three years, and Fabre several cases. Out of twenty-four cases of mumps Fournié saw no less than five instances of recurrence; Krugelstein, Guasco, and Logerais each report one case. In the epidemic of 1892–93 Catrin[5] noted nine recurrences and two relapses (one after eighteen days, the other after three months) out of one hundred and fifty-seven cases of mumps. Busquet[12] reports three cases of recurrence; one patient had five attacks, three on the left side and two bilateral; another had two attacks, and the third had three attacks. In each of these cases diplococci were found in the blood. From the statistics of the French army we find two

cases of a second attack in 1885, two in 1887, two in 1889, three in 1890, five in 1891, and three in 1892, with two recurrences in one person. The period separating the two attacks of the same disease is a very variable one, being sometimes rather short and at other times long. In Catrin's cases there was one recurrence at the end of one year, two after two years, three after four years, one after five years, one after seven years, and one after ten years.

Symptoms.

Incubation.—As is the case with most infectious diseases, mumps has a period of incubation, of latent germination in the organism. Most authors are agreed that this period is of quite long duration, being greater than the corresponding stage in almost all of the other contagious diseases. It is usually stated to be on an average three weeks. Rilliet and Lombard give the following figures as the result of an analysis of 29 cases: In 1 case the period of incubation was 8 days; in 11 it was 19 to 20 days; in 13, from 20 to 22 days; in 1, between 23 and 26 days. Eight days must be regarded as the minimum, although Demme speaks of one instance in which it was 4 days only, and Picot and d'Espine state that the period varies between 4 and 26 days. According to d'Heilly the duration is from 18 to 22 days. Dukes says, basing his opinion on a study of 42 cases, that the period of incubation varies from 18 to 22 days, although he speaks of exceptional cases in which the period was lengthened to 23, 24, and 25 days. In an epidemic in India Jobard noted the outbreak of the disease on shipboard 23 days after having left land. Antony has reported cases in which the period was 26, 28, and 33 days. Merklen has seen 2 cases of 25 and 26 days' duration respectively. Roth mentions 3 cases seen in Bamberger's service in which the period following contagion was 18 days, and Pearse also fixes the same period as the duration of the incubative stage. Henoch says that this period ranges from 14 to 22 days. In a small hospital epidemic following the entrance of a child with mumps into the wards, Cadet de Gassicourt records the first cases as having occurred on the twentieth day. On May 6th, 1892, I was called to see a boy of four years who had a double parotid swelling dating from the previous evening. This child had been to school for the last time on April 16th, and assuming that he had acquired the contagion on that day, the incubation lasted 19 or 20 days; but as the infection may have occurred before his last day at school, the period of incubation may have been longer than 3 weeks.

Invasion.—In most cases the invasion is gradual and without

noisy symptoms, a slight swelling of the parotid gland being the first indication of the on-coming disease. However, exceptions to this rule occur, and I have seen patients taken suddenly with a chill, high fever, headache, delirium, etc. When the patients have been under observation and have been carefully watched during the period of incubation, we are often able to note the occurrence of prodromic symptoms. These are, however, usually so slight that they are commonly overlooked by those having the care of the child. Rilliet and Cadet de Gassicourt speak very briefly of the prodromes of mumps; Barthez and Sanné noted prodromes in 230 out of 540 cases in a school epidemic. Catrin saw them in 102 out of 157 cases; in 44 cases they consisted in chills and malaise, in 58 cases in malaise only; among individual symptoms he noted night sweats 41 times, epistaxis 14 times, tinnitus aurium 18 times, earache 8 times, joint pains 15 times, herpes labialis 4 times, and syncope twice. Sore throat and fever are the usual initial symptoms. In 24 cases Fournié noted pharyngitis and angina 15 times; the same symptoms were observed by Bourgeois in 19 out of 61 cases, by Jourdan in 16 out of 60, by Madamet in 11 out of 56. At Bayonne in 1891 three out of four of the soldiers attacked had sore throat at the beginning. Catrin mentions this symptom as having been seen in 62 out of 100 patients. Fever is a nearly constant symptom at the beginning of mumps.

I have noted a mode of invasion which is rather frequent in the case of children, namely, by an attack of otalgia. A young patient is suddenly seized with very severe pain in the ear which may keep him awake during the night; this pain is usually unilateral, and in the morning there is seen to be a swelling in the parotid region on the same side. On June 27th, 1892, a child, eleven and a half years old, was brought to the dispensary to be treated for a pain in the left ear which he had had for five days. The pain was severe enough to prevent sleep and it was accompanied by fever, headache, and anorexia. On examination I discovered a marked swelling beneath the left ear and extending down the neck. The other side presented nothing abnormal, the disease remaining unilateral. There was no congestion of the buccal mucous membrane, but the saliva reddened litmus paper. On May 11th, 1892, a girl, ten years old, of good physique, was brought to me on account of a soft, diffuse, painful swelling of the left parotid gland. The child could not open the mouth, there being an actual trismus preventing mastication. This swelling had been preceded for three days by marked somnolence, fever, redness of the face, anorexia with coated tongue, headache, etc. On the two days before I saw her she had had epistaxis. Her brother, five years old, had been complaining of earache for two

days, and there was already apparent a slight parotid swelling. Another brother, six and a half years of age, had suffered from excruciating pain in the ears two weeks before, preceding an attack of mumps.

Parotid Swelling.—This is the most important symptom as regards both frequency of occurrence and conspicuousness. It may be the first symptom to appear, and in any case is a very early sign, and as it causes such deformity of the face it cannot pass unperceived. Its seat is the space between the mastoid process and the ascending ramus of the jaw, that is to say, at the location of the parotid gland. Here the skin is seen to be tense, the swelling is smooth, not hard, and moderately painful on pressure and during movements of the jaw, which it serves to impede. From its point of origin the swelling encroaches on the neighboring parts without any line or furrow by way of demarcation.

The two parotid glands are affected, not simultaneously, but one after the other after an interval of one, two, or three days. Bouchut said that mumps (*oreillons*) had no singular, which is, however, not strictly correct. Unilateral mumps is far from being exceptional, and in some epidemics *oreillon* (in the singular) is the rule. Rizet, of Arras, noted a single parotitis fourteen times and a double one eight times in twenty-two cases. Rilliet, of Geneva, found a proportion of one unilateral to six bilateral cases, and one simultaneous involvement of both parotids to every three cases of successive attack. He distinguished three degrees of swelling, as follows: (1) A very moderate swelling, with slight soft engorgement of the gland, and but little deformity of the face; (2) a very noticeable prominence in the parotid region, which is swollen out, tense, and painful on pressure, and sometimes the skin is red; (3) the tumefaction in the parotid region is marked, extending in every direction and disfiguring the patient greatly. Rilliet and Barthez say that they have seen this tumefaction carried so far that the tumor beginning in the parotid region extended almost to the extremity of the clavicle, giving to the head and neck a pyriform appearance, and causing the patients to look grotesque and to be almost unrecognizable.

In the epidemic of Arras some instances of enormous swelling were recorded by Rizet. Three adult patients presented a frightful deformity of the face; in two the parotid and submaxillary glands were so swollen that the patients had no resemblance to human beings, and the third had such a tremendous tumor that he was unrecognizable even by his most intimate friends. In the case of a lad of sixteen years, the right parotid alone was involved, but this was so enlarged that in less than five days the swelling had reached

the sternoclavicular articulation on that side; the skin was shining and there was a feeling as if fluctuation were present. In two weeks all swelling had disappeared and there remained only an engorgement of the cervical glands in the form of a chain in the neck, but this also disappeared in the course of two months. Henry reported the case of a little girl of five years in whom the swelling extended from the parotid forward to the middle line of the neck. In a young boy I once saw engorgement of the salivary glands and œdema of the surrounding parts assume such a size that the swelling on each side met the other in the middle line of the neck forming a double chin of a most hideous appearance. In this case the submaxillary and sublingual glands were involved, and I believe that the lymphatic glands were also swollen to a certain degree.

It is easy to determine that the swelling actually involves the salivary glands and not alone the cellular tissue surrounding them; it is located in front of the tragus, behind the ascending ramus of the maxilla over which it rises. When the glandular projection is very marked we may palpate directly the parotid gland on which we may distinguish the lobulation and uneven surface. The skin is but little changed, but slightly adherent, and not greatly congested. Sometimes it presents a red shining appearance which may lead us to suspect an abscess or erysipelas.

Pressure is more or less painful. Rilliet has marked out three painful points: One at the level of the temporomaxillary articulation; another below the mastoid apophysis; the third over the location of the submaxillary gland. The patients complain but little of spontaneous pain, but only of stiffness and inconvenience. Sometimes, however, there are very severe pains, neuralgic in character, which radiate to a distance in all directions. The most severe pain which I have seen in mumps was located in the ears, either in the external auditory canal or in the tympanum; this is sometimes so severe as to make the children cry out and to prevent them from getting any sleep. The pains are usually stronger during the prodromic period than after the declaration of the disease. The separation of the jaws, restricted by the swelling, is always limited and painful, and mastication becomes difficult, if not impossible; thus the taking of solid food must be foregone, the patients limiting themselves to liquids, and sometimes even fluids cannot be taken except through a tube. It is in the cases of this kind that we see the trismus mentioned by Rilliet and which I have also noted occasionally, which interferes with both mastication and articulation. The jaws, pressed closely one against the other, as in tetanus, can scarcely be separated so as to admit the tip of the tongue. Without being tetanized, however, the movements

of the jaws may be so interfered with as to cause a very peculiar and almost characteristic pronunciation.

The swelling may extend not only downwards but also upwards towards the eyes and forehead. Gailhard has noted a swelling of the eyelids and of the subconjunctival connective tissue, accompanied by chemosis. Karth and Pognon have remarked upon a slight degree of exophthalmus. We shall refer to this again when speaking of the ocular localizations of mumps. Henoch has observed once or twice a dilatation of the temporal and periorbital veins which he thinks was due to compression of the facial vein by the enlarged parotid.

The parotid swelling is in general of short duration; it reaches its height in two or three days and then begins to decrease in size, being normal again in three or four days more. Cases have been observed, however, in which the duration was much longer, and even in which there remained a permanent chronic parotid enlargement (Merklen). E. Albert[13] has seen the swelling become permanent in certain cases of relapse. Two regimental trumpeters suffered from relapse, due apparently to the efforts made by the men to play their instruments. Following these relapses there remained a notable enlargement of the parotid, in one case for eight months, in the other for ten months.

Submaxillary Swelling.—The swelling does not always remain confined to the parotids, but may invade also the submaxillary glands. It may even begin in and remain limited to these glands (submaxillary mumps). Catrin saw the submaxillary glands participate in the morbid process 71 times in 137 cases; Antony, 15 times in 42 cases; Fournié saw a swelling of these glands in almost all of his cases. Vacher has reported 3 and Wertheim 4 cases in which the submaxillary glands were alone involved; Fabre noted 2 cases of exclusive submaxillary localization during an epidemic in which 700 persons were attacked; Amodru saw 4 cases of submaxillary mumps in a school epidemic attacking 19 girls. Laveran reports a case of submaxillary mumps complicated with orchitis: A patient was admitted to the infirmary at Val-de-Grâce with measles. While still in the hospital he was attacked during the night with a submaxillary swelling which lasted for two days and then began to diminish in size. There seemed to be some doubt as to the diagnosis because of the immunity enjoyed by the parotid glands, and it might have been regarded as a case of double adenitis simply, had it not been for the fact that two days later the two testicles became swollen and painful; at the same time the temperature rose considerably, but fell again on the fourth day. I have recently seen a case in which the swelling was limited to the submaxillary glands, and another in which

it remained in this region for some time after the parotid trouble had subsided. On November 28th, 1892, a little girl, four and a half years of age, of generally good health, was brought to me for a fever with anorexia which had come on two days before. The day before she was brought to me her mother had noticed a swelling of the cheeks looking like that accompanying an aching tooth, but there was nothing wrong with the child's teeth. When she came to me there was a bilateral swelling in the submaxillary region, more marked on the left than on the right side. On passing the finger down the cheek and beneath the inferior maxilla an olive-shaped body, about the size of an almond, could be felt, which could be nothing else than the submaxillary gland. The parotid glands were not swollen at all.

Sublingual Swelling.—That the sublingual salivary glands may participate in the morbid process seems to be undeniable, though some have held that it does not occur. Indeed, I have seen at least one very distinct case of sublingual mumps. On November 30th, 1892, a girl, eleven years old, was brought to me at the dispensary for treatment for a subhyoid swelling which had appeared the previous morning without being preceded by any very marked disturbances of the general health. Below the chin was a symmetrical swelling, not especially painful on pressure. The day before, according to the story told by the mother, there had been a slight enlargement in the parotid and submaxillary regions, but when I saw the girl there was none, the only thing visible being the tumefaction in the floor of the mouth. Some very small and painless lymphatic ganglia could be felt on the sides of the neck. Digital pressure caused slight pain, not only under the chin but also at the angle of the jaw and in front of the ear. The only durable swelling having been that of the sublingual glands, it is certainly permissible to regard the case as one of sublingual mumps. Henoch reports a less clear case. Under the name of subglossitis or inflammation located beneath the tongue in the floor of the mouth, he describes a disease which seems to affect the sublingual glands and which may be an abnormal form of mumps. The subhyoid region is swollen and œdematous, the tongue is pressed upwards, and the jaws are separated. The disease terminates by resolution in seven or eight days.

The Buccal Mucous Membrane.—Upon examining the mouth of a patient suffering from mumps we sometimes find nothing abnormal, at other times there are more or less appreciable changes visible. The mucous membrane is often dry and a little red, the gums are swollen and covered with an opaline pultaceous deposit, and the tongue is coated. We have had occasion, in speaking of the prodromes, to note the mention by many writers of a sore throat. Some

authors have claimed, however, that there is occasionally a true buccal exanthem. Guéneau de Mussy especially insists upon this point, and says: "Mumps, as Trousseau has so justly remarked, bears the strongest resemblance to the eruptive fevers, and if my personal observation is not at fault this resemblance is made still stronger by the coexistence of a congestion with tumefaction of the buccal mucous membrane, most marked in the vicinity of the posterior molars, towards the inner surface of the cheeks, around the orifice of Steno's duct, and on the anterior part of the palatine vault. This has appeared to me to be a true exanthem, the tegumentary manifestation of the disease." He adds that he has found this eruption in three cases of mumps, in one of which swelling of the submaxillary and sublingual glands replaced that of the parotids.

J. Moursou has noted a tumefaction of the orifice of Steno's duct, which he says is almost always present, appearing in the form of a nipple about the size of a small haricot bean, markedly congested and with some ecchymotic points around the meatus. The canal itself can be felt, he says, by the finger as a thick and hard cord. Granier says that there is hyperæmia not only of Steno's duct but also of those of Wharton and Rivini, as shown by a projecting dark red ring at the orifice of each of these ducts. Laveran, however, holds that these lesions are an exceptional occurrence and are of little significance.

I have published two cases of erythematous and pultaceous stomatitis in children suffering from mumps. This stomatitis is located chiefly on the gums, but I have never observed any abnormal appearance at the orifice of Steno's duct. In the first case there was a very pronounced redness of the buccal mucous membrane, especially marked on the gums, accompanied by acidity of the secretions and an abundant salivation. In the second case the stomatitis was more severe in character; it was at first erythematous but soon became pultaceous with quite thick deposits on the gums and internal surfaces of the cheeks. There was salivation, and bleeding occurred from the gums. On the seventh day the child was well, both parotitis and stomatitis having disappeared. I have since seen cases of similar buccal lesions, but I do not think the appearance deserves the name of an exanthem.

Salivary Secretion.—In a large number of cases I have noted that the saliva gives an acid reaction with litmus paper, though in some cases the secretion remains neutral. There is more or less disturbance of the salivary secretion in the majority of cases of mumps. Rilliet and Laveran, however, both state expressly that there is neither salivation nor dryness of the mouth in mumps, and if dryness

does exist it may well be due to the fever present. Bouchut says that the pain, swelling, tension, and redness of the parotid are always accompanied by dryness of the mouth and throat and pain on swallowing, and he remarks that in cases in which the disease is confined to one side the dryness is present only on that side. He attributes the dryness to salivary retention, due, he says, to the swollen condition of Steno's duct which becomes obliterated and like a hard cord. Galland notes in a large number of cases dryness of the mouth at the beginning and during the height of the disease with an abundant salivation, apparently critical in its nature, at the moment of resolution. Trousseau speaks of the difficulty in mastication dependent in part upon the pain, but chiefly upon the disordered secretion of saliva, which in some cases is completely suppressed, so that even in convalescence, he says, the patient is obliged to drink constantly while eating, a mixture of saliva with the food not taking place. Clarke has also observed dryness of the mouth together with roughness and hardening of the buccal mucous membrane in consequence of the absence of the saliva. Simon and Prautois have recorded a case of increased salivary secretion occurring as a sequel to mumps. The flow was so abundant and persistent that it was necessary to restrict it by the administration of atropine.

General Symptoms.—The fever and other general symptoms vary greatly in intensity in the different cases. There are mild, abortive forms in which there appear to be no general symptoms whatever. It is especially in complicated cases that the fever is marked, but it is usually present even in the mildest attacks. Catrin insists especially on this point. "The symptom which we have noted most commonly at the beginning is fever, which many observers have nevertheless regarded as exceptional or as present only in connection with more or less grave complications. Fabre, of Commentry, in twenty-seven cases out of fifty-eight, noted the occurrence of violent fever, even with chills, although there was no orchitis; Fournié noted fever in seven out of twenty-four cases; Prozorowski, in an army epidemic, saw but three apyretic cases; Lichtenstern says that there is always fever at the commencement, and Gerhard says that there is always more or less elevation of temperature. . . . The fever is moderate, sometimes even inappreciable without the use of a thermometer, since, as Comby justly remarks, 'the patients are confined neither to the bed nor to the room, but come and go, eat and digest.' This author assigns to the fever a duration of four or five days, and says that the defervescence is rapid, agreeing also with Gerhard that the disease is never absolutely apyretic. This is also our opinion, and in the army, where the men are immediately isolated upon the

first symptoms of mumps, this observation can be made better than elsewhere. . . . In an epidemic studied by us in 1892–93 out of 143 cases in which the temperature was taken, apyrexia was noted in but 38; in 46 cases the fever lasted one day, in 39 two days, in 15 three days, and in 5 four days. The temperature varied between 38° and 40° C. (100.4° and 104° F.). Of the apyretic cases 2 men only were in the second day of the disease when first seen, 13 were in the third day, 4 in the fifth day, 7 in the sixth, 3 in the seventh, and 1 in the tenth day. When the parotids were affected successively at an appreciable interval, the fever was often observed to light up again coincidently with the swelling of the second gland. It is therefore our absolute conviction that cases of mumps in which there is no elevation of temperature must be very exceptional. At the same time that we were studying this epidemic of mumps there occurred one of measles, and we noticed that the apyretic cases, or at least those in which the fever was very moderate, were as common in measles as in mumps. In one disease as in the other the benignity of the symptoms at the outset might be so pronounced that the men did not regard themselves as sick or they did not enter the hospital until the eruption had appeared or until the parotids were swollen, that is to say, at a time when the fever had subsided."

The fever is usually moderate in degree, especially in children whom often it does not prevent from getting out of bed, going about where they will, and engaging in their usual occupations and games. In some cases, however, it is intense from the beginning, and is accompanied by restlessness, the typhoid condition, and delirium. In such cases we may be led to suspect the presence of one of the eruptive fevers or of typhoid fever, but at the end of four or five days defervescence occurs, gradually by lysis; sometimes, however, the fall is rapid, and the pulse becomes slow and irregular. It is especially in cases complicated by orchitis that we see high fever and general symptoms of sometimes an alarming character. The fever may be terminated by profuse sweats, at first limited to the parotid regions and later becoming generalized. A critical polyuria has also been reported.

Convalescence is sometimes quite prolonged, the patient coming out pale and emaciated from a disease which is of short duration and apparently benign. Rilliet says that he has seen several patients who had not recovered their usual health by the end of two or three weeks, and were astonished that such a mild disease could cause such a physical depression. Some authors have spoken of an enlargement of the spleen. All these symptoms afford evidence, if

such were needed, that mumps is a general disease the action of which is not confined to one or two of the glands of the body, but affects in some measure the entire organism.

Course and Duration.

The course and duration of mumps vary according to the form and the gravity of the disease. There may be abortive cases which can scarcely be recognized as mumps; the swelling is very slight and ephemeral and the general symptoms are imperceptible. These abortive forms would not be recognized at all did they not occur in the course of epidemics of mumps and were they not sometimes complicated by orchitis. The mild form of the disease lasts scarcely three or four days; those of moderate intensity last at least a week. The duration of the complicated forms is very indefinite. The duration of the disease is of course longer when the two parotids are attacked successively after an interval of several days.

The affection may be prolonged also by the occurrence of relapses. In a patient under the care of Karth there were no less than five distinct attacks, each one marked by fever and general symptoms. The first attack, which was the gravest of all, affected the salivary glands, the kidneys, and the spleen; the second involved the lacrymal glands; the third, limited to the parotids, enabled a diagnosis of mumps to be made; the fourth was marked by a swelling of the submaxillary glands; in the fifth attack the lacrymal glands were alone attacked. Each successive attack in this series was less grave than its predecessor.

There are chronic forms of mumps in which the parotid engorgement persists for months. The usual termination of mumps, however, is by a resolution, as complete as it is rapid, of the parotid swelling. It has been said that suppuration never occurs in mumps, and this is true in the great majority of cases, but there are nevertheless exceptions to the rule. The microbe of mumps is not pyogenous by nature, but we may well suppose that it favors by its presence the entrance of pyogenic organisms, such as the streptococcus and the staphylococcus, which we know to be often present in the saliva even of healthy persons. Indeed, experience shows us that suppuration may occur, not only of the glands originally involved in mumps (the parotids) but also of those affected by metastasis (the testicles). We shall return to this subject when studying the genital localizations of mumps and also the complications of the disease in the following section.

Extrasalivary Localizations and Complications of Mumps.

Genital Localizations.

There is no disease which menaces more the genital organs than does mumps. Next to the salivary glands the seminal glands are the most frequently involved in the morbid process, and this so frequently that we may regard their participation as a special localization of the disease rather than as a complication.

Orchitis.—Hippocrates was the first to mention the orchitis of mumps. This localization, while rare in children, is common in young adults whose genital organs are developed and in full activity. Nevertheless its occurrence is not unknown in children and even in infants. Henoch never saw an instance of this localization in a child, and neither have I, and Rilliet says that the youngest subject he has seen was fourteen years old; Barthez and Sanné, however, out of two hundred and thirty cases, saw three children twelve years old, and seven in youths between fifteen and seventeen years of age. Debize reports the case of a boy, thirteen years old, who, following a parotid swelling, accompanied with high fever (104° F.), had orchitis on the right side, and fell into a typhoid state. Fabre cites a case in a boy of nine years, and Cérenville one in a child of four years. In general we may say that medical literature furnishes very few cases of the orchitic complication of mumps in children, and we may regard this complication as practically never seen in epidemics in primary schools, although it ceases to be a wholly negligeable quantity in epidemics in colleges and seminaries; but it is in army epidemics especially that it is to be feared. In an epidemic studied by Saucerotte (1785–86), all the gendarmes who were attacked by mumps suffered from orchitis. Noble, in the epidemic occurring on board the *Ardent*, saw twelve cases of orchitis out of twelve cases of mumps among the marines. At Châteauroux (1832) most of the adults attacked with mumps suffered also from orchitis. Thierry de Maugras, in the epidemic of Mascara, saw 22 cases of orchitis in 76 of mumps; Rizet, of Arras, 10 in 22; Widal 50 per cent.; Juloux, 14 in 35; Chatain, 9 in 37; Laurens, 32 in 118; Bussard, 13 in 28; Sorel, 15 in 35; Gérard, 13 in 44; Madamet, 7 in 56; Servier, 26 in 105; and Jourdan, 11 in 61. In 699 cases of mumps recorded in fourteen army epidemics, there were 211 cases of orchitis, or about 30 per cent. Catrin has collected a large number of cases from many sources and finds 1,965 cases of orchitis in 10,601 cases of mumps, that is, about one case of

orchitis to every six of mumps, instead of one to three as in the statistics of army epidemics, above quoted, collected by Laveran.

It has been said that the orchitis of mumps may be distinguished from that of gonorrhœa by an exclusive localization in the parenchyma of the glands, the epididymis remaining unaffected. Catrin, however, disputes this assertion and says that in forty-three cases observed by himself he always found the epididymis engorged, and when it was possible to observe the case from the start it was always seen that the epididymis was affected before the parenchyma of the testicle; in one case, the epididymis alone was affected to the entire exclusion of the parenchyma of the organ. The same author claims that there is an abortive form of orchitis occurring sometimes in mumps, manifested by some vague pains in the testicle, either spontaneous or excited by pressure, and occasionally there may even be a slight swelling of the testicle or of the epididymis. These attacks, he says, are never followed by atrophy of the testicle. The temperature may be slightly elevated, but there are never any appreciable general symptoms, and the local manifestations are ephemeral and so slight that the patient may not mention them at all unless special inquiry is made. The occurrence of these abortive cases of orchitis has been noted by others also, among them Chauvin, Fournié, Viela, Talon, Vedrennes, Logerais, and Sorel.

The orchitis declares itself generally from the sixth to the eighth day following the parotid enlargement, at the moment that this is disappearing, as if the disease left this gland to invade another (metastasis). But the theory of metastasis is not applicable to all cases, for the orchitis may show itself before the subsidence of the parotid swelling, or may even precede it or finally may be the sole manifestation of the mumps. Gérard has noted the appearance of orchitis when there was no parotid swelling and after the complete disappearance of the latter. Grivert has seen two cases in which the orchitis came on ten days and three weeks respectively after the subsidence of the parotid affection.

Sometimes the orchitis is announced by grave general symptoms, such as fever, restlessness, delirium, or convulsions. Sometimes it creeps on insidiously and would pass entirely unperceived did not the increase in the size of the testicle incommode the patient and direct his attention to this part. In two or three days the testicle increases to several times its normal size and becomes hard, heavy, and troublesome; the scrotum is red and tense; the organ is not very painful on pressure. There are sometimes pains extending along the spermatic cord into the abdomen; exceptionally there are symptoms of peritonitis present. It has been said that the orchitis always

occurs on the same side as the enlarged parotid, but this is not so, for it is often crossed or bilateral. A mild parotitis may be accompanied by orchitis just as readily as one of great severity.

The proportion of cases of double to those of single orchitis varies in different epidemics. In Geneva Rilliet found 4 cases of double orchitis out of 23; in the unilateral cases there were 13 on the right side and 6 on the left. Juloux in 14 cases of orchitis found 1 in which both testicles were affected. Laurens, in 32 cases of orchitis, found 6 double, 17 on the left side, and 9 on the right. Jourdan found 1 double case in 11 of orchitis, and Servier 2 in 26. On the other hand Rizet saw 7 cases of double orchitis to 3 of single at Arras, and 5 double to 3 single at Montpellier. Taking the average of all these statistics we find that unilateral orchitis is eight times more frequent than bilateral.

What is the course of the orchitis of mumps? Usually at the end of two, three, or four days the tension begins to diminish, the inflammatory œdema subsides, and the gland is seen to be large and but slightly sensitive on pressure. Then gradually it returns to its normal size, but in a certain number of cases we find on examination at a later period that there has been an atrophy of the testicle. This is the black spot in mumps in the adult. Hamilton (1761), Murat (1803), and J. Frank referred to atrophy of the testicle following mumps, and later Dogny (1828) reported 27 cases observed in soldiers. Rilliet noticed a diminution in size of the testicle in 2 cases following recovery from mumps, in one of which the organ was reduced to one-half of its normal size. Grisolle reports 4 cases observed in his own practice, and he remarks that this accident would be regarded as less common if the patients were kept under observation a long time, for the atrophy is a late accident and progresses slowly and without active symptoms. Chatain followed up 9 cases of orchitis and found 3 of them terminating in atrophy of the testicle. Chauvin saw 6 cases of atrophy out of 16 of orchitis. Juloux examined the testicles of 14 soldiers two months after they had recovered from orchitis and noted a diminution in size of the testicle in all. In 32 cases of orchitis Laurens found 16 of atrophy; the gland was smaller by one-fourth in 7 cases, by one-half in 7, and by three-quarters in 2. Sorel, examining his patients seven or eight months after recovery from orchitis, found 7 in whom atrophy had occurred. Gérard, in 11 cases examined fifteen months after recovery, found a diminution in consistence in nearly all, a diminution in volume in 4, and a pronounced atrophy in 2; in one of these cases both testicles were reduced to the size of a bean, and there was also a diminution in virility. Madamet found a slight atrophy in 4 of 7 soldiers examined

three months after an attack of orchitis. Servier examined 23 men six months after recovery and found atrophy of the testicle in 12; the atrophied testicles were about the size of a large haricot bean, were rather hard, and were wholly insensible to pressure, which did not cause any of the peculiar testicular sensation. In one case he found hypertrophy of the testicle. Jourdan examined 11 soldiers in the fourth and fifth months following an attack of orchitis and found in 5 the testicles reduced to the size of a bean, in 3 the organs were reduced about one-half in size and were quite soft, in 2 the diminution was slight, and in 1 there was a hydrocele. Catrin examined 37 men from seven to eleven months after recovery, and found 16 cases of marked atrophy, 5 of softening, and 4 in which the testicles first became atrophied and later returned to their normal volume. Of 13 who had had double orchitis 6 had normal glands and 5 had double atrophy. In the statistics of the army he found among 175 cases of orchitis complicating mumps, 51 in which atrophy had occurred, that is to say, 1 in 3.5, or 29.14 per cent. In his own statistics he found 1 case of atrophy to every 2.3 of orchitis, or 43.24 per cent., but says that if he had counted among his cases those of abortive orchitis he would have obtained nearly the same figures as those derived from the general statistics, that is to say, 1 atrophy in 3 cases of orchitis, or 32 per cent. From another study of statistics Laveran obtains figures which are a little higher than these. Thus, in ten epidemics there were 163 cases of orchitis recorded with 103 of testicular atrophy.

The results of this testicular atrophy, especially when double, may be quite grave, for there may be loss of virility, sterility, and an effeminacy of the constitution, as shown by the eunuch voice, enlargement of breasts, etc. These extreme consequences of atrophy of the testicles are exceptional, but impotence and sterility are not rare. The possibility of this accident darkens considerably the prognosis of mumps in the adult.

The orchitis of mumps may have other and much more rare terminations than atrophy. Hornus[14] reports a case in which suppuration occurred. The patient was a soldier, twenty-two years of age, who suffered from double orchitis during an attack of mumps; the glands suppurated, peritonitis supervened, and the man died; the pus passed up along the spermatic cord and gave origin to the peritonitis. In other cases the orchitis may become chronic just as we have seen that parotitis may also pass into a chronic state. Martens has reported a case in which the orchitis of mumps passed into a tuberculous orchitis and this was followed by pulmonary tuberculosis.

Certain anomalies have been noted in respect to the appearance of

the orchitis in mumps. In the course of an epidemic we may see alongside of ordinary mumps cases of febrile orchitis not associated with parotitis, similar to those cases which Morton has described under the name of febris testicularis. I have seen a few examples of this incomplete, abortive mumps, and certain military surgeons have described analogous cases under the name of rheumatismal orchitis, primary infectious orchitis, etc. Kovacs has recently reported two cases of orchitic mumps without parotitis. Laveran does not hesitate to admit that unilateral or double orchitis may constitute the only manifestation of mumps, there being absolutely no enlargement of the salivary glands. In an epidemic at Châteauroux in 1832, there were several cases of orchitis without any swelling of the parotid glands either before or after the testicular affection. The same thing was observed in an epidemic at Geneva, according to the reports of Julliard, Rilliet, and Mayer. Desbarreaux-Bernard reports seven cases of this abnormal form of mumps; in one family a patient had an attack of orchitis at the same time that his brother suffered from parotitis. At Dantzig, among twenty-nine soldiers suffering from orchitis only ten had parotid enlargement, and in the remaining nineteen no parotid swelling could be detected at any period in the course of the disease. Other similar cases have been reported by Rizet, Boyer, Debize, Vidal, Jacob, Sorel, Laveran, Chauvin, Servier, and others.

The orchitis may appear as the first symptom of mumps, preceding the parotid swelling. There is here simply an inversion in the chronology of accidents. The army surgeons above mentioned report a fairly large number of such cases. On the other hand Grivet has recorded certain cases of retarded orchitis, the testicular trouble coming on some time, weeks or months, after the disappearance of the parotid swelling.

Urethritis and Prostatitis.—The testicle is not the only portion of the genital apparatus which may suffer in the course of an attack of mumps. The urethra, the prostate, and the seminal vesicles may, although rarely, present more or less marked symptoms of inflammation. In ten cases of orchitis reported by Barthez and Sanné there were five in which there was a yellowish viscous discharge from the urethra. These patients recovered promptly enough. Other authors have noted rare instances of urethritis in mumps in which the presence of the gonococcus was negatived. Gosselin saw a young man, twenty-one years old, suffering from orchitis due to mumps, who had a well-marked prostatitis, as shown by tumefaction of the gland, which lasted three days. In the case of a man, twenty-nine years old, who was suffering from orchitis and epididymitis as a result of mumps, I was able by rectal examination to determine the

existence of marked tenderness of the corresponding half of the prostate and of the seminal vesicle on this side. If it were made a matter of routine to note the condition of the prostate by rectal examination in every case of orchitis complicating mumps we should doubtless find that more or less participation of the prostate in the morbid process is quite common.

Ovaritis.—In women also the glands of the genital apparatus may be affected in mumps, but this complication is less common than the analogous trouble in man, and the inflammation is apt to be less intense. In two women of twenty-nine and thirty-two years respectively, Rizet observed intense pains which seemed to reside in the ovaries. Niemeyer, without reporting any specific instances, speaks of pain in the ovarian region occurring in the course of mumps. Meynert found a week after an attack of mumps in a girl, sixteen years of age, a rounded, painful swelling in the right iliac fossa; this had disappeared at the end of three weeks. Bouteillier noted the occurrence of iliac pains, soon becoming limited to the right side, in a woman, twenty-four years old, who was suffering at the time from mumps. In the right fossa a tumor somewhat elongated transversely could be felt, which was mobile and painful on pressure; recovery took place in two weeks. Vogt has related to me the following case: A girl, eleven years old, who had had an attack of mumps, complained of distress in the right side of the abdomen, and on deep palpation a tumor the size of an almond could be felt; this disappeared at the end of nine days. Such are the rare instances of ovaritis complicating mumps which I have been able to collect. It is a matter of some astonishment that the testes muliebres should so commonly escape a process which attacks with such predilection the seminal glands in man.

Inflammation of the Labia and Vulval Glands.—A metastasis to the labia majora, already noted by Laghi in the preceding century, has been observed by Rilliet in the person of a woman thirty-six years of age. In this woman, a swelling of the labia majora appeared on the fifth day of an attack of mumps, and disappeared in the course of three or four days. Peter believes that this swelling is due to an inflammation of Bartholin's glands. In a case of this kind Gailhard saw the process go on to suppuration.

Mastitis.—Several observers have noted this complication of mumps. Trenel reports three such instances. In the first a girl, eighteen years old, had parotitis which subsided on the fifth day, when suddenly the fever lighted up and the mammæ became swollen and painful; on the seventh day this swelling began to diminish, profuse sweats appeared, and recovery ensued. The second case was

that of a girl of fifteen years in whom a painful swelling of the breasts appeared on the fifth day of mumps, while the parotids were yet enlarged; recovery took place on the seventh day. The third patient was a pregnant woman, thirty years of age; on the sixth day, while the parotid swelling was diminishing, the breasts became large and tender; on the eighth day sweating occurred and the woman recovered. Rochard, Cavallini, J. Franck, Roche, Cullen, and Sir A. Cooper have mentioned swelling of the breasts in women suffering from mumps. Jobard noted a considerable enlargement of the breasts in an East Indian woman who was suffering from mumps, and in whom the parotid swelling reappeared when the mastitis subsided. Rizet mentions the occurrence of mammary engorgement in a little girl of five years during an attack of parotitis. He also reports an engorgement of the mammary glands in two soldiers as a result of mumps; in one of these there appeared four accessory glands which remained visible for ten days, and a serous fluid could be expressed from the nipples. Marchand also observed in the case of a soldier suffering from mumps an engorgement of the mamma from which a whitish fluid could be expressed; the same man had an attack of orchitis.

Thus we see that all parts of the genital apparatus and even its accessories are exposed to attacks by mumps.

Non-Genital Localizations and Complications.

Thyroid Gland.—A thyroid complication has been noted by Matignon[15] and Guelliot.[16] The case of the latter was that of a young girl, twelve years old, who was taken on May 11th, 1889, with a moderate swelling of the right parotid gland. On May 14th the neck began to increase in size, and on the 16th there was seen to be a horseshoe-shaped swelling in the front part of the neck, most prominent on the right side; the right lobe of the thyroid gland was the size of a pigeon's egg, the left being smaller. There was no peripheral œdema, the patient had no pain, fever, or submaxillary adenitis. On May 17th the thyroid began to diminish, and the following day had resumed its normal size.

Lymphatic Ganglia.—Cases of submaxillary, preauricular, or cervical adenitis are not rare as a complication of mumps; they are ordinarily temporary only, though Rilliet has reported one case in which a scrofulous adenitis followed an attack of mumps. Catrin had recorded fifty cases of adenitis of variable location, several being of a genian adenitis in front of the masseter. Lafforgue[17] has noted adenitis marking the beginning of mumps in five men from twenty-

one to twenty-three years of age, the primary submaxillary adenitis preceding by forty-eight hours at least the parotid engorgement and disappearing with the latter. Occasionally suppuration occurs in these cases of adenitis complicating mumps. Madamet has reported a persistent retro- and sub-maxillary adenopathy in five soldiers. Jourdan observed swelling of the cervical lymphatic ganglia three times in sixty-one cases of mumps. Rizet saw in a soldier with mumps a chain of enlarged glands in the neck which persisted for two months. Since my attention has been called to this point I have very frequently, in children, seen a more or less lasting, but benign, cervical adenopathy occurring as a sequel of mumps.

Suppurative Parotitis.—Suppuration in the course of mumps is a relatively rare occurrence if we consider the entire number of cases, but absolutely there are very many instances of this accident on record. Barjon[18] saw three cases of suppurative mumps in the same epidemic. In one of these cases there was a gangrenous abscess with burrowing of pus along the vessels of the neck, but recovery eventually occurred. In such cases there has probably been a secondary infection, analogous to what we sometimes see in typhoid fever, smallpox, pneumonia, measles, etc. Busquet and Ferré, in a paper read at the Bordeaux Medical Congress in 1895, drew especial attention to the relation existing between streptococcal inflammations and mumps, reporting four cases of erysipelas following parotitis. Stoicesco[19] has reported a case of suppurative mumps in a man of thirty years and another in a woman of thirty-three years. Dionis noted in the course of an epidemic among the ladies of St. Cyr in the last century that suppuration occurred in almost every case of mumps, but there is some doubt whether these were true cases of mumps. In an epidemic affecting nearly one hundred persons at La Pelisse, Maslieurat saw suppuration but once, and Laveran's experience was the same in an epidemic which he saw in Paris. Bucquoy, out of several thousand cases, saw only two which terminated in suppuration. Ferrand reports one case in a child of seven years, in which a bacteriological examination revealed the presence of streptococci.

Digestive Tract.—The digestive manifestations of mumps have received but little attention from students of the disease. I have already spoken of the buccal exanthem, the pultaceous stomatitis and erythematous sore throat, in which, however, there is nothing of a specific character. The coated tongue, anorexia, and constipation are too common and insignificant to require description. Thierry de Maugras has noted catarrh of the biliary passages in some cases

of mumps seen by him in 1848, and Holdman has spoken of the occurrence of jaundice.

Respiratory Apparatus.—Œdema of the glottis, fatal in a few instances, has been noted as a complication of mumps. I have observed a case of pulmonary congestion with profuse hæmoptysis, and Merklen has recorded a case of pulmonary apoplexy with diaphragmatic neuralgia. Holdman reports a case of pulmonary embolism of parotid origin. Boinet has seen bronchopneumonia. Ferrand saw a fatal attack of pleurisy complicating mumps in a lady of advanced age. Although these complications affecting the respiratory organs are rare, they may be of extreme gravity. Tourtelle reports two fatal cases of œdema of the glottis, and Jacob one of œdema of the larynx. In a case of the same sort, Pilatte[21] performed tracheotomy and the patient recovered.

Circulatory Apparatus.—In addition to the functional disturbances which may be noted, such as tachycardia at the beginning of the disease, a slowing of the pulse at the period of defervescence, and arrhythmia, cases have been observed of peri- and endo-carditis. Gachon[22] has reported a case of pericarditis complicating mumps, and he says that the affection in such cases is usually dry, unaccompanied by other complications, and not commonly fatal, but it may coexist with endocarditis. It is only when it occurs in patients who are free from rheumatic taint that it deserves to be regarded as a true complication of mumps. Jaccoud has reported two cases of endocarditis coming on during an attack of mumps; in one recovery took place, in the other the condition became chronic. This form of endocarditis is located for the most part at the mitral orifice. Bourgeois[23] and Catrin have reported cases of the same complication. We must take care not to mistake an anæmic murmur for the expression of an organic lesion.

Rheumatism.—We pass very naturally from a consideration of the cardiac complications of mumps to that of the numerous instances of arthropathy which have been mentioned by writers on mumps. Trousseau has recorded the occurrence of articular pains in mumps which were similar to those observed in scarlatinal rheumatism. Jourdan, in a study of sixty-one cases, noted four of articular pains in the shoulders, elbows, and wrists. These arthropathies, which are unmarked by swelling or effusion into the joints, usually disappear in the course of a few days. In some of the reported cases there is reason to suspect that true rheumatism was the underlying condition. Thus Rilliet saw acute rheumatism follow an attack of mumps in two brothers, but one of these had suffered from true rheumatism some years previously, and the parotitis served only as

an exciting cause to light up the old trouble. In other cases, however, it seems as though the attack of mumps really determined a sort of infectious pseudorheumatism. A few joints only are involved at a time, fixation in consequence of the arthralgia occurs, the process passes along the synovial sheaths and invades the bursæ (the prepatellar bursa in a case reported by Bergeron), there is moderate fever, hydrarthrosis occurs, etc. As a rule this form of rheumatism terminates in resolution, but suppuration may occur in some cases. Sometimes the rheumatic symptoms precede the occurrence of the parotid swelling. In one case of arthritis complicating mumps Catrin found the diplococcus in the exudate.

Nephritis.—In thirty-nine cases in which the urine was examined every two or three days, Catrin found albuminuria in twelve, that is to say, in about thirty per cent. Pratolongo noted the occurrence of anasarca in certain cases of mumps which was similar in all its characters to scarlatinal anasarca. Renard reports three young soldiers suffering from mumps who had albuminuria and anasarca, and he attributed the complication, from which all recovered perfectly, to a renal congestion similar to that of the parotid gland. In a more recent epidemic the same observer saw several cases of albuminuria of which three terminated fatally. In a fourth case the patient had already had mumps, and at the time of observation had a very considerable œdema of the scrotum and lower extremities, from which he recovered perfectly. Jourdan saw a case of mumps complicated with hæmaturia; in this case there was also a swelling of the thyroid gland. Colin twice saw anasarca in soldiers suffering from mumps. One of these patients was a very robust and ordinarily healthy man, twenty-four years of age. On October 23d, 1875, while on guard, he felt discomfort in the testicles, which soon after became swollen, the right more than the left. On the day following this there appeared a swelling in the left parotid region unaccompanied by any marked fever. The face then became puffy and the œdema spread over the entire body. The urine contained albumin. Purgatives and diuretics were given, but no improvement took place. On November 6th he noted a disturbance of the sight; the visual acuity was diminished, the papilla was œdematous, and there were spots on the retina. On November 10th the patient complained of dyspnœa and headache with insomnia, and on the 12th it was noted in the report that the cephalalgia was so intense as to cause the man to cry out with the pain. On the following day he had an epileptiform convulsion followed by coma. The amount of urine passed did not exceed 300 gm. in the twenty-four hours; it contained 10 gm. of urea and 22 gm. of albumin per litre. Four leeches were applied to

the mastoid process, and the blood removed was found to contain urea and fat. The man had other epileptiform convulsions and died on November 21st. At the autopsy the kidneys were found to be enlarged, the cortical substance was yellow in appearance and contained numerous white spots. Under the microscope there was seen to be interstitial proliferation, the tubules were filled with fibrinous and granulo-fatty casts. The spleen was enlarged, the heart was hypertrophied, and there was hydrothorax with pulmonary œdema.

In a case reported by Karth [3] there was intense albuminuria following a period of anuria. Jaccoud mentions the same complication, and Gagé [24] made it the subject of a thesis. Although it is more rare in the child than in the adult, nephritis has nevertheless been observed in young subjects as a complication of mumps. Croner has reported a case of the kind occurring in a child of six years. In November, 1883, during an epidemic in Berlin, a boy, six years old, was seized with a parotid swelling on the left side, preceded by quite a sharp fever. This parotitis terminated in resolution, but five days later, the child not having yet left his bed, there was a new access of fever and the parotid again enlarged. This engorgement disappeared rather quickly, but the child remained languid and had no desire to get up. Fifteen days after the onset of the mumps there was noticed an œdema of the eyelids and of the dorsal surfaces of the hands and feet, together with a slight degree of ascites. The urine, which was excreted in small quantity, was bloody and contained a large proportion of albumin. Six days later, while the nephritis was progressing favorably, the temperature rose again, the lymphatic glands at the angle of the left jaw together with the neighboring connective tissue became swollen, and the urine again contained blood and albumin. In a week these phenomena had again subsided, but now the ganglia on the right side took their turn. After this the albuminuria persisted for five weeks and the beginning of convalescence was delayed until about two months after the onset of the trouble.

Skin.—Various cutaneous symptoms have been observed in mumps. G. Morard [25] has observed in the case of two soldiers with mumps an eruption resembling measles, consisting in red elevated spots, disappearing on pressure, over the trunk and limbs. The eruption occurred without any elevation of temperature. B. Pailhas[26] has reported a scarlatiniform eruption in a girl of thirteen years, a vesicular eruption in a girl of seven years, and a varioliform papulovesicular eruption preceding by three days the parotid swelling in a boy seven years old. In a boy nine years of age Guelliot found multiple areas of painful œdema unaccompanied by albuminuria. The child was thin and frail in appearance and had suffered

severely from gastroenteritis in early childhood. Having been out one cold day, he complained of malaise on returning to the house, and had a chill; that evening mumps appeared. The following day (December 17th) he had pains in the wrists and a white œdematous swelling of the hands and forearms, without any fever. The day succeeding this he complained of pain in the right leg and there was slight œdema here with several petechiæ; there was no albuminuria. On December 20th orchitis appeared on the right side, and there were some ecchymoses in the right eyelid. The following day the left arm was the seat of a soft, white, painful swelling. On the 22d there was some improvement, but the day following this orchitis appeared on the left side, the prepuce became œdematous, and there was also a painful œdema of the scalp. On December 25th there was œdema of the right eyelids, on the 26th painful œdema of the right calf, and on the 28th œdema of the dorsal surface of the feet. Anæmia was marked, but no albuminuria was found at any time. On the 31st convalescence set in and the boy made a good recovery.

Nervous System.—The nervous complications of mumps are very interesting and sometimes very grave. As in all the infectious diseases we may have ataxo-adynamic phenomena, restlessness, delirium, carphologia, and convulsions. Sir Astley Cooper saw a child die in delirium after a sudden resolution of the parotitis. Ordinarily the nervous accidents precede or accompany orchitis. In addition to the ordinary nervous accidents mentioned, cases have been reported in which there occurred hysteriform, epileptiform, or maniacal attacks, but in these cases there was most frequently a preëxisting neurosis to account for the unusual symptoms, the attack of mumps acting only as an exciting cause of the paroxysm.

Lannois and Lemoine[27] lay special emphasis on the meningitic and cerebral complications of mumps. They recall a case reported by Hamilton of a young man, twenty-two years of age, who died in a furious maniacal paroxysm during an attack of mumps, one of Gillet concerning a man who died after having had delirium and two attacks of syncope, one of Behr in which recovery followed coma with stertorous breathing accompanied by fever, and another of Lynch in which the patient had delirium with sensory illusions and tinnitus aurium, in all of which the symptoms were acute and transitory. They then dwell especially upon certain cases in which the accidents were persistent, namely, aphasia and paralysis. Healy reports the following case which occurred in Monro's service: A child, fifteen years old, of very nervous constitution, contracted mumps. He appeared to have recovered, when delirium and fever supervened and orchitis came on. On the evening of the fifth day the tempera-

ture was 107° F., the pupils were insensible to light, and there was obstinate constipation. The following days the delirium was so furious that it was necessary to restrain the patient. On the eighth day coma appeared, the pulse was filiform, the temperature fell a little (103° F.), but there were crises of furious delirium in which the child tried to bite those about him. No headache was complained of and there was no vomiting. Walking was difficult for some six months after recovery, there being incoordination and uncertainty. The speech was troubled, the child was very emotional, and he had agraphia. Another case was in the person of a lad of seventeen years who had mumps with orchitis on the right side; he was suddenly seized with furious delirium and had aphasia and right brachial monoplegia with anæsthesia; he recovered. Sorel saw a corporal, twenty-four years old, admitted to the hospital on account of orchitis complicating mumps; the temperature was over 107° F., and there was delirium followed by great depression, and then aphasia which continued for fifteen months. In a case seen by Lannois and Lemoine aphasia and right hemiplegia occurred. The patient was an artilleryman who was admitted to the infirmary for double mumps, which disappeared promptly. One week later the man was seized with vomiting and lost consciousness; he was found in a semicomatose condition, and examination showed the presence of right-sided hemiplegia with hemianæsthesia and a slight degree of contracture. The face was paralyzed on the left side. When the patient recovered consciousness he was unable to articulate a single syllable and had to employ signs to express his wants. The fever was 102° to 103° F., but the pulse was only 60 to the minute. A dose of sulphate of sodium was given and ten leeches were applied to the mastoid processes. There was retention with overflow of urine and it was necessary to use the catheter. Finally power of movement returned and the aphasia disappeared. All these symptoms, according to Lannois and Lemoine, were due to hyperæmia of the meninges or to a meningoencephalitis.

We do not deny that cases of encephalitis occurring in mumps are in some cases due to congestive or inflammatory lesions of the meninges, but when we see mania, melancholia, hysteria, or epilepsy coming on in patients during an attack of mumps we must look behind this disease to an hereditary nervous taint, or sometimes to alcoholism.

Paralysis.—After mumps, as after diphtheria, there may be either spinal or peripheral paralysis, ordinarily curable; some interesting instances of this have been reported by Joffroy[28] and other writers. A little girl four and a half years old was brought to Joffroy on

account of a flaccid paralysis of the four extremities; she could neither walk nor stand erect; there was absence of tendon reflexes as well as of galvanic and faradic contractility. The bladder and rectum were not affected. The diagnosis of infantile paralysis or of Pott's paralysis was rejected. Joffroy considered the possibility of a diphtheritic paralysis but could obtain no history of this disease; the child had had mumps, however, five weeks previously. Eight days after the beginning of the disease the child had lancinating pains in the arms and then an intense itching of the genital organs; the pains afterward extended to the thigh and legs and there was formication of the parts. Three weeks after the appearance of the mumps paraplegia was marked, and there was also a slight but intermittent albuminuria. Thirty days from the commencement of the disease the paralysis had involved the upper extremities. A tonic treatment was instituted, and stimulating frictions were made twice a day, iodide of potassium being given internally. Soon the power of movement returned in the lower extremities and then in the upper, and the albuminuria diminished. Three months later the child had almost entirely recovered.

Chavanis[29] has reported the case of a man fifty-five years old who had mumps and orchitis with high fever and prolonged delirium. Fifty days after the onset of the disease he had lumbar pains, cephalalgia, hebetude, and weakness of the legs, especially of the left; there was a sensation as if the left foot were too short and he dragged the leg on this side. In walking he had a sensation as if the soles of the feet, especially the left, were of rubber. There was sweating on the left leg but not on the right. One year later there was melancholia with same hebetude, but the patient was able to work better than before. He had frequent headaches and general weakness persisted, there were involuntary seminal emissions and impotence was almost complete. The spine was painful on pressure and the lower extremities, especially the left, were paretic. There were cramps in the calves and formication in the left foot. The paralysis was never sufficiently pronounced to prevent walking, but there was merely a difficulty with a feeling of weight, and the left leg often gave way under him. Two years later recovery had taken place, the sadness disappeared and work had again become easy; nevertheless, the lower limbs were not so strong as formerly and the left leg especially remained weak. This case is remarkable on account of the severity of the initial symptoms and the extremely long duration of the paralysis. On December 19th, 1895, I saw a child, three and a half years old, who had had mumps a month previously. For a week he had had a weakness in the lower extremities, which made walking impossible.

The reflexes were abolished and there were pains in the knees. The child recovered. Revilliod [30] has reported the case of a boy of seven years who had symptoms of paralysis a few days after an attack of mumps. There was flaccid paralysis of the four extremities, most marked in the lower limbs, together with complete left facial paralysis and paralysis of the right hypoglossal nerve and of the velum palati. Deglutition was difficult and respiration was slow and sighing, but the sphincters were intact. Subcutaneous injections of strychnine were given, together with stimulating frictions, electricity, and salt baths. In two months the paralysis disappeared but the reflexes were not restored.

The Special Senses.—The organs of sight and of hearing are quite frequently affected in mumps. Hatry of Lyons has noted a diminution in the acuteness of vision, photophobia, lacrymation, and injection of the papilla. He mentions especially palpebral œdema which has also been seen by others. Boas has reported a case of amblyopia due to mumps in a girl of seven years. Dor reports a case of dacryoadenitis due to the same cause in a child three years of age; the patient also had lacrymation and photophobia. Adler, Hirschberg, and Marc Dufour have observed similar manifestations and have even described mumps of the lacrymal gland. Leriche [31] has made this the subject of a thesis. The symptoms consist in orbital pains radiating to the forehead and to the temporal regions, the eyelids are swollen and œdematous, covering the eyeball, and there is also a chemosis. A diagnosis might be made of simple conjunctivitis, but on careful examination we find an oblong, smooth, hard swelling, painful on pressure, at the site of the lacrymal gland. In from twenty-four to thirty-six hours the œdema diminishes and the pains disappear. In the treatment of this affection warm fomentations, astringent collyria, eye washes of boric acid, and scarification have been recommended.

The aural manifestations are less rare and more interesting; they are also more grave, for they frequently result in incurable deafness. Catrin has made a careful study of this complication. "The disease presents itself with constant and uniform characteristics which give it a special physiognomy which has been well described by Ch. Eloy. The occurrence of deafness is rapid, often unexpected and almost sudden, and is ordinarily an early symptom, but one case having been reported in which it occurred after two weeks. Even when it is unilateral it has no correspondence with the seat of the parotitis; the influence of sex, age, and the gravity of the original disease seems to be nil. The affection may or may not be accompanied by general symptoms, such as noises in the ears, disturbance of equilibrium, vomiting, insomnia, and finally vertigo, which latter

may persist for months or years, or may become attenuated, leaving a simple vertiginous condition, which is increased by any causes which in themselves tend to produce vertigo, such as looking from a height and the like. We need not stop to examine here the value of the theories which have been advanced to explain these symptoms, but we hold frankly to the opinion of Fournié that there is a direct impression of the auditory centres, or perhaps we may add, of the auditory nerve. The absence of lesions and the inefficiency of therapeutic measures suffice to distinguish this vertiginous deafness of mumps. St. John Roosa and Tsakyroglous claim to have obtained some improvement, as regards the vertigo at least, by the administration of sulphate of quinine. Roosa in forty-five hundred cases of ear disease saw ten of labyrinthine affection following mumps, but some of these cases are rather indefinite. In one instance, for example, there had been scarlatina, mumps, and measles, and it is difficult to say what part each of these affections had had in producing the deafness. In another case a woman thirty-five years old, who was already deaf as a result of scarlatina, found the deafness increased after an attack of mumps. Menière in 1887 reported four cases presenting the same symptoms, the same rapidity of evolution, and the same obstinate incurability. Kipp has seen two cases of the sort. Connor in 1884 collected thirty-three cases, among them some benign ones, and he thought the lesions were located in the semicircular canals. Finally Tsakyroglous[32] reports two cases, in one of which recovery occurred, and another case of suppurative otitis. The treatment most commonly employed has been by electricity, iodide of potassium, revulsions, and finally pilocarpine, which latter, however, does not seem to have met the expectations of cure which the first trials of it aroused.

In addition to these cases of incurable deafness, other instances have been recorded at the onset or during the course of mumps of temporary deafness accompanied by pain, but usually recovered from spontaneously or in consequence of the employment of the most simple remedies.

Prognosis.

The prognosis of mumps is generally benign, for no one dies of the uncomplicated disease. Out of four hundred and ninety-six cases occurring in the French army during the years 1862–65 there was but one death. In 1869 one death from mumps is recorded among the troops in Algeria. Since that time we find noted occasionally one or two deaths among thousands of cases, and were it therefore not for the untoward complications, notably orchitis, to which the sufferer

from mumps is exposed, the disease would scarcely be deserving of serious attention. The prognosis varies greatly according to the age and sex of the patient. In the child the disease is always very benign; it develops quietly without complications, and the testicles are practically never affected. In the adult male, as we have seen above, the question is a very different one. We notice the difference very clearly when an epidemic attacks both children and adults. Among fourteen children and two adults suffering in the same institution at Geneva, d'Espine and Picot saw complications in the adults only and in both of these. The complications vary also in different epidemics; while Rizet, at Arras, saw ten cases of orchitis out of twenty-two of mumps, Vogel, at Munich, saw orchitis only once in hundreds of adult cases of mumps. Besides orchitis, nephritis, and localizations in other parts of the genitourinary apparatus, death has been observed to result from œdema of the glottis. Bougard[33] reports the case of a man, fifty-four years of age, who died asphyxiated in consequence of compression of the larynx and trachea by the enormously enlarged parotid glands.

In some epidemics children may suffer greatly. Trenel says that he has seen two children die from mumps. Demme, of Berne, in 117 cases coming under his observation in the course of a single year, saw 8 of great severity, and 2 in which death resulted from gangrene of the parotid glands. In 3 children there were cervical abscesses, in 2 an acute nephritis, in another suppurative otitis media with perforation of the drum membrane and meningitic symptoms.

The influence of sex is as great as that of age. While the genital complications are very frequent in men, and sometimes very grave as well, in women they are exceptional, and the recorded instances of ovaritis, inflammation of Bartholin's glands, and mastitis complicating mumps are few in number.

Leaving aside the occurrence of the rarer complications, we may sum up the question of orchitis as affecting the prognosis in mumps in the following conclusions of Laveran: "1. Orchitis constitutes the principal danger of mumps in the adult male. 2. In the adult male orchitis complicates mumps twice in every five cases. 3. The orchitis accompanying mumps ends seven times out of ten in atrophy of the testicle. 4. In those cases, fortunately very rare, in which the atrophy affects both testicles, absolute impotence is the inevitable result." We may dispute these figures and look upon the proportions given by Laveran as too high, but in a general way his conclusions may be regarded as sufficiently exact.

Diagnosis.

When we are in the presence of an epidemic of mumps the recognition of the disease is a matter of great ease, even of those cases which are incomplete or abortive. A parotid swelling, however small and ephemeral, can scarcely be overlooked at such a time, and even in the absence of a parotid enlargement, the occurrence of an orchitis or of some other less usual localization of the disease will be readily referred to its true cause. Error is possible, however, even when the parotid gland is swollen, and the affection has been confused with preauricular or submaxillary adenitis, with tonsillitis, and with inflammatory or toxic parotiditis.

Preauricular adenitis occupies the same site as mumps, and it may sometimes accompany this affection and persist after the parotitis has disappeared. It is seen, however, to be superficial, subcutaneous, making a rounded projection of moderate size, and on palpation we feel a rounded and strictly circumscribed gland, unless perchance the inflammation has invaded also the neighboring connective tissue, in which case we obtain a doughy feel, pain on pressure or spontaneously, and later fluctuation. The adenopathy is often multiple, and we can then feel several glands forming an irregular mass which is sometimes continuous with a chain of ganglia in the neck. This chain is unilateral.

When the mumps is limited to the submaxillary gland we must be still more careful not to confound it with adenitis in the same regions. In order to prevent any error we must not only inquire into the history of the case, but must also examine with care the condition of the mouth and of the teeth, and observe the shape and general appearance of the swelling. Even when there may be some doubt at first all uncertainty will be quickly removed by the further progress of the case. If it is one of simple engorgement of the submaxillary glands from mumps the enlargement will be speedily reduced in the course of a few days, but if we have to do with an adenitis the condition will last for some time and even suppuration may occur.

Certain cases of tonsillitis or of diphtheria may, in consequence of the swelling which they cause at the angle of the jaw, give rise to a suspicion of mumps; but an examination of the throat will suffice to establish the correct diagnosis.

True parotiditis complicating infectious disease is almost always unilateral; it is painful, distinctly inflammatory and phlegmonous, and often suppurative.

In addition to these acute cases of parotitis there may be chronic

ones which will sometimes cause more or less embarrassment. In 1882 I reported a case of hypertrophy of the parotid glands due to lead poisoning.[34] Following lead colic or other symptoms of saturnism we may see the parotid glands enlarge and form two symmetrical tumefactions at the angles of the jaws, soft and painless, persisting indefinitely without change; this very unchangeableness of the symptoms will serve to distinguish such enlargements from mumps. In addition to these cases of lead parotiditis there have been reported others caused by copper or mercury, or due to uræmia, etc. In the cases in which mumps passes into the chronic state the disease may possibly be confounded with one of these forms of toxic parotiditis.

Raymond Johnson[35] has described a special form of parotid swelling which merits a brief description. He reports five cases (three in children and two in adults) of a swelling and induration of the parotid, coming on usually during a meal, which persisted several weeks. There was pain during mastication, and in one instance the gland suppurated. In one case repeated relapses occurred during a period of two or three years. This swelling was due to a retention of the saliva in consequence of obstruction of Steno's duct. In two cases pressure on the enlargement caused a discharge of saliva from Steno's duct.

In all these cases of chronic enlargement of the parotid gland the diagnosis is usually not difficult; but it is different with certain instances of parotid engorgement which are acute and temporary and which sometimes present a very close resemblance to mumps. I refer now particularly to what has been described by Villar under the name of mumps-like iodism, iodic mumps, etc. A man entered the Hôpital St.-Louis on February 3d, 1883, on account of multiple ganglionic tumors with enlargement of the spleen. Some days after admission he took two spoonfuls of a solution of iodide of potassium, containing forty-five grains of this salt, in the course of the day. About nine o'clock, two hours after having taken the second spoonful, he was seized with sneezing, which lasted for about half an hour, then followed vomiting of the food which had been taken, and respiratory oppression. After this attack, which was of short duration, the patient complained of pain in both parotid regions, and swellings appeared here, becoming very considerable within five minutes. At the same time headache came on of such intensity as to prevent the patient from sleeping. The following day, twenty-four hours after the first dose of iodide of potassium had been taken, the skin was hot, the tongue coated, the pulse rapid, there was an eruption on the forehead and nose, the patient complained of headache, and he seemed to be much depressed; but the most striking symptom was

the swelling in the parotid regions. On the right side this swelling was limited above by the lobule of the ear, in front by the anterior edge of the masseter muscle, and behind by the mastoid apophysis; below, the swelling was gradually lost in the submaxillary region. On the left side the tumefaction was much greater, involving the whole of that side of the neck. On both sides the skin was red and hot and there was pain on pressure over the swollen parts. Although there was nothing abnormal in respect to the testicles, Villar thought that the case was one of mumps, but Balzer regarded it as one of parotid localization of iodism in an individual with an idiosyncrasy as regards iodine. The administration of the iodide was stopped, and the following day the swellings had subsided very markedly and a complete cure resulted in three days. Some authors, among them Regnier and Miss Bradley, have noted similar cases, and I have myself seen a very marked instance. The patient was a woman, twenty-five years of age, who entered my service in the Hôpital Tenon for treatment for syphilis. On the first day she took thirty grains of iodide of potassium, and at the end of twenty-four hours had œdema of the eyelids, coryza, lacrymation, salivation, and an equal and symmetrical enlargement of the parotid gland on each side, which greatly resembled mumps. The iodide was stopped and the parotid engorgement subsided. Facts of this nature being now well recognized, the occurrence of a swelling of the parotids in consequence of iodism should not lead to an error in diagnosis.

The diagnosis is especially difficult in the abortive forms in cases in which the parotid enlargement is wanting, or in those in which the usual order of symptoms is disturbed, as when the orchitis appears first, or those finally in which the physician's attention is drawn away by abnormal localizations of the disease. It is very reasonable to suppose that a case of orchitis occurring without any characteristic symptoms of mumps might not be referred to its true cause, when there are so many other causes of this condition, such as gonorrhœa, tuberculosis, or traumatism, to which the inflammation of the testicle might equally be due. A young man, twenty-five years of age, pale and emaciated, and suffering from night sweats, presented himself to me for advice concerning an enlarged testicle. Both the epididymis and the body of the testicle were affected, being hard and uneven. No mention was made of any previous affection of the parotid gland. I diagnosed tuberculosis of the testicle and instituted treatment accordingly; the patient recovered in a very short time, and I then discovered that his trouble had been orchitis due to the poison of mumps.

When the disease first and exclusively manifests itself in enlarge-

ment of the submaxillary glands we more naturally think of an adenitis than of mumps, and it is usually quite easy to find some pimples on the skin, dental caries, or some buccal lesion to account for the occurrence of this submaxillary swelling. In forming our diagnosis we must have regard to the symmetry of the two swellings, to the suddenness of their appearance, to their shape, and to their location, which is exactly that of the submaxillary salivary glands. Finally the further course of the disease will soon suffice to put all doubts at rest. We must remember, however, that submaxillary adenitis is not in itself rare in cases of true mumps. I have seen several such cases in which the ganglionic engorgement was very marked and persisted after the mumps had disappeared. Barthez and Sanné have reported a case in which the enlarged glands following an attack of mumps became the seat of a strumous process.

Cases of localization of mumps in the sublingual glands are even more difficult of diagnosis, for we may be led to regard the affection as acute ranula or a phlegmon in the floor of the mouth, surgical affections which have nothing in common with mumps.

When the general symptoms are so severe as to mask the local manifestations, or when they precede the latter by an appreciable interval of time, possibly several days, when we find hyperpyrexia (104° to 106° F.), restlessness, delirium, convulsions, or disquieting cerebral symptoms, we shall not be likely to think of mumps so long as the local symptoms remain absent, and we shall rather fear the beginning of one of the grave infectious diseases, such as scarlatina, diphtheria, typhoid fever, or even meningitis. The mistake will be even more readily made in the absence of an epidemic of mumps at the time. On the other hand when an epidemic is in full swing the danger will lie in the other direction, for the tendency at such a time is to refer every illness of whatever nature to the account of the prevailing disease.

Treatment.

In this section we shall have to consider first the prophylaxis of mumps and then the curative treatment of the disease, the latter being divided into the treatment of mild cases and that of the more grave ones.

Prophylaxis.

Certain physicians, especially those who have much experience in the management of diseases of children, are wont to decry the utility of all precautionary measures, basing their opinions on the fact that mumps is such a benign affection in early childhood. Laveran goes

even further and contends that it is an advantage, for boys at least, to have their attack of mumps early in life so as to enjoy immunity later, at a period when the disease is a distinct menace through its tendency to attack the genital organs. But orchitis is not the only complication to be feared, for there yet remain nephritis, otitis, and permanent deafness, conditions which threaten children as well as adults. We ought then to insist upon isolation in schools, families, and hospitals as soon as the disease has declared itself in a child. The period of isolation should be at least three weeks, but need not be longer than one month in simple cases. We have seen above that mumps is especially contagious in its early stages, but that it may also be transmissible during the height of the attack and even during convalescence. According to Pearse, the contagious period lasts three weeks, and if we order a quarantine of from twenty-five to thirty days we shall be doing all that is necessary. Sir Thomas Raven succeeded in preventing an epidemic of measles in a school of four hundred and fifty scholars by sending every child into the hospital immediately upon the appearance of the least parotid swelling. The first case was followed by two others on the eighth day and by one other on the twenty-second day, and the entire epidemic was limited to these four cases.

Even though some authorities may doubt the utility or advisability of prophylactic measures in the case of children, no one calls their necessity into question in the case of adults, and military surgeons are always very solicitous to limit the spread of mumps among the troops in camp or garrison. Every soldier attacked, or even suspected, must be at once isolated; but isolation alone is not sufficient and it is necessary to disinfect thoroughly all garments and other objects which have been in contact with the sick, and also the localities in which they have been confined. The microbe of mumps is very tenacious of life and persists for a long time in garments and bedclothing. As contagion through a third person is possible, physicians in charge of the sick should take all necessary precautions in order not to convey the contagium in their persons or clothing from the sick to the well.

Disinfection, however, is not always efficacious. In the epidemics of 1888 at Périgueux, of 1889 at Bourges, of 1891 in the Eleventh Regiment of Chasseurs, and of 1892 at Mans, despite the most energetic disinfection the disease blazed up again from its ashes. In such cases it would be proper to move the troops temporarily, and to air their quarters thoroughly and leave them empty for a certain time. Fumigation with burning sulphur and sprays of sublimate have been shown to be ineffectual. All movable objects should be subjected to

disinfection by steam under pressure, and the apartments and barracks should be fumigated with formic aldehyde.

Treatment of Mild Cases.

In the management of simple cases hygienic measures suffice. The patient should be made to keep to the room and even for a time in bed. Repose is absolutely necessary, for not only does it favor resolution of the parotid swelling, but it also tends to prevent the appearance of complications, especially of orchitis. Catrin insists especially upon this point. "A certain number of observers have remarked that fatigue seems to favor the occurrence of orchitis. Chauvin has seen simple congestion become transformed into actual inflammation after a long march; Servier recommends that these patients be sent at once to the hospital, and Laveran says that those who are obliged to follow laborious pursuits and who continue their labors after the onset of mumps are more subject than others to orchitis, and swelling of the testicles in such cases assumes greater proportions. The same result is seen when the patients leave the bed too soon. We have been led to the same conclusions through our experience in 1892. At the beginning of the epidemic which we had occasion to study at that time, following the general opinion that the average duration of mumps is from eight to ten days, we discharged our patients after a rest in the hospital of twelve, ten, or even eight days; but we often saw these same patients return after four, six, or eight days, in most cases with a relapse more grave than the original attack or with orchitis or some even more serious complication. Such a case was that of a man who, after a stay of an entire month in the hospital for a very severe attack of mumps, returned four days after his discharge with suppurative otitis media and suppurative arthritis of the knee. In another case a man who left the hospital on February 9th, after a stay there of eighteen days, returned on February 27th with a relapse complicated with œdema of the eyelids, vertigo, cephalalgia, tinnitus aurium, and albuminuria. In two other cases an orchitis occurred in soldiers who were obliged to take up the fatiguing duties of the service immediately upon their discharge from the hospital. Frequently also we have seen orchitis occur in patients who were disobedient and who by reason of the mildness of their attack did not deem it necessary to follow the injunctions of the physician. This may possibly be the reason why some authors have come to the conclusion that the mildest cases of mumps are those which are most liable to be followed by orchitis. Even when the patients are not kept strictly in bed, most physicians

advise that they remain indoors, even in the mildest cases. The action of cold may cause or hasten the occurrence of certain complications."

In addition to rest we may prescribe a restricted diet, especially a milk diet. If there is a catarrhal condition of the digestive tract, as is usually the case, we should prescribe a purgative, such as calomel, scammony, jalap, Seidlitz powder, or the like. Hufeland advised the exhibition of an emetic, and also the application of a mercurial plaster to the swollen parotid gland. If the tumefaction is very marked, and the skin is red, hot, and painful, we may order inunctions of opium and belladonna ointment or other soothing applications. The affected parts should be covered with a thick layer of cotton. If there is trismus or difficulty in opening the jaws the patients should be advised to drink through a tube.

In order to prevent secondary infection through the nose or mouth, suppurative mumps, otitis, adenitis, etc., we must not fail to insist upon the systematic employment of antiseptic lotions in the mouth, throat, and nose. We may make the toilet of these cavities three or four times a day by means of sprays or vapor; the use of boiled water, boric-acid solutions, or solutions of naphthol will ordinarily suffice.

We do not recommend the employment of counterirritation over the parotids with the object of preventing metastases, as Hamilton thought could be done when he advised the use of flying blisters over the enlarged parotid glands. There should be no vesication, no mustard plasters, no ice even, and no massage of the tumors; covering them with cotton batting is all that is necessary or advisable.

Treatment of Grave and Complicated Cases.

In severe cases of mumps accompanied by high fever and adynamia we must resort to more active measures than those just described. In such cases I have seen much benefit from cool baths (64° to 68° F.) repeated three or four times in the twenty-four hours. We should also prescribe Todd's potion (cinnamon, brandy, and syrup), acetate of ammonia, or strychnine or caffeine hypodermically, not forgetting cinchona or quinine. In a case accompanied by hyperpyrexia, Jaccoud prescribed bromhydrate of quinine for the fever and tartar emetic for the glandular engorgement. The temperature fell immediately to 100° F. and then to normal, but two days later it rose again to 104° F., and the right testicle became enlarged. These severe cases are very difficult to treat effectually.

There is little to do for the orchitis beyond rest and emollient applications, for a too active interference may be actually dangerous.

Eisenschütz endeavored to hasten the cure of orchitis by massage and succeeded only in provoking the appearance of grave general symptoms. We must also abstain from leeches, scarifications, and blisters.

Czerniky and Emery Desbrousses have spoken favorably of the use of jaborandi, and they report two cases in which an infusion of 2 gm. of the fresh leaves in 200 gm. of water brought about resolution of the orchitis. Martin injects pilocarpine under the skin with, as he claims, equally favorable results. Sorel, however, resorted to the employment of jaborandi in four cases and in three saw atrophy of the testicle supervene. Vedrennes, whose experience was similar to this, has no faith whatever in the remedy. It is a question whether any better results would be obtained by the exhibition of salicylate of sodium, as advised by Henderson in doses of ninety grains, or of pulsatilla which has been recommended by Ducastel.

When the testicle is soft and in process of atrophy, we may try massage, punctate cauterizations, electricity, douches, etc.

For the deafness following mumps iodide of potassium, quinine, and pilocarpine (Dundas Grant) have been advised, as also catheterization of the Eustachian tube.

In cases of paralysis, we may prescribe stimulating frictions, salt baths, electricity, massage, and strychnine.

For the nervous symptoms, pseudomeningitis, we must resort to the wet sheet, the bromides, musk, and ether.

In cases in which a grave anæmia persists after recovery, we may give iron, quinine, cod-liver oil, iodotannic syrup, etc. Much benefit may also be derived in suitable cases from a change of air, sojourn in the country, a course of sea baths, and other tonic measures.

Bibliographical References.

1. Hippocrates: Upon Air, Water, and Situations; upon Epidemical Diseases; and upon Prognosticks. Translated by Francis Clifton, M.D. London, 1752.
2. Jules Comby: Les Oreillons, Paris, 1894.
3. Karth: Thèse de Paris, 1883.
4. Ollivier: Bulletins de l'Académie de Médecine de Paris, June 23, 1885.
5. Catrin: Gazette des Hôpitaux, June, 1895.
6. Busquet et Ferré: Congrès de Médecine de Bordeaux, 1895.
7. Mecray and Walsh: Medical Record, September 26, 1896.
8. Michaelis: Berliner Gesellschaft für innere Medicin, 1897.
9. Roth: Münchner medicinische Wochenschrift, 1886.
10. Séta: Thèse de Paris, 1869.
11. Busquet: Bulletins de l'Académie de Médecine de Paris, October 5, 1897.
12. ——— Revue de Médecine, September 10, 1896.
13. E. Albert: Revue de Médecine, October, 1895.

14. Hornus: Archives de Médecine et de Pharmacie Militaires, 1894.
15. Matignon: Gazette des Sciences Médicales de Bordeaux, 1890.
16. Guelliot: Société des Hôpitaux de Paris, 1893.
17. Lafforgue: Médecine Moderne, September 16, 1896.
18. Barjon: Revue Médicale, 1895.
19. Stoicesco: Presse Médicale Roumaine, 1895.
20. Holdman: Journal of the American Medical Association, 1887.
21. Pilatte: Bulletin Médical, June 8, 1890.
22. Gachon: Thèse de Montpellier, 1887.
23. Bourgeois: Thèse de Paris, 1888.
24. Gagé: Thèse de Paris, 1892.
25. G. Morard: Nouveau Montpellier Médical, June 1, 1895.
26. B. Pailhas: Médecine Infantile, June 15, 1895.
27. Lannois et Lemoine: Archives de Neurologie, 1886.
28. Joffroy: Progrès Médical, November 20, 1886.
29. Chavanis: Bulletin Médical, November 8, 1891.
30. Revilliod: Revue Médicale de la Suisse Romande, 1896.
31. Leriche: Thèse de Paris, 1895.
32. Tsakyroglous: Monatsheft für Ohrenheilkunde, October, 1893.
33. Bougard: Journal de Médecine de Bruxelles, 1866.
34. Jules Comby: La France Médicale, 1882.
35. Raymond Johnson: Harveian Society of London, April 16, 1896.
36. F. Villar: La France Médicale, June 2, 1887.

INDEX TO VOLUME XIII.

Acne pustulosa, diagnosis of, from smallpox, 450
Adenin, 111
Adenitis, diagnosis of, from mumps, 595
in mumps, 584
Air, expired, leucomaïns in, 124
probably free from microbes, 137
smallpox infection carried by the, 400
typhoid fever infection carried by the, 303, 316
Alantiasis, 46
Albuminuria in mumps, 587
in smallpox, 437
Alcohol, indications for, in the treatment of smallpox, 482
predisposition to infectious disease increased by, 460
Alexins, 215
Alexocytes, 271
Alkaloids, animal, ptomaïns incorrectly so called, 10
bacterial, 9
putrefactive, 9
America, introduction of smallpox into, 393
Amœba coli, 357
dysenteriæ, 357
Amphikreatin, 124
Anasarca in mumps, 587
Ankylostomum duodenale, water-borne, 291
Anthracin, 13
Anthrax, bacterial poison of, 81
intrauterine infection of, 150
orrhotherapy in, 242
symptomatic, development of, favored by the bacillus prodigiosus, 174
orrhotherapy in, 247
Antitoxic action of serum different from the preventive power, 274
Antitoxin, 215, 239, 270
conversion of toxin into, by electricity, 107
mode of action of, explained in the case of antivenomous serum, 267
of diphtheria, 262
origin of, 270
theory of immunity, 215, 220, 228
Arginin, 122
Arsenic poisoning, water-borne, 287
Ascaris lumbricoides, water-borne, 290
Asellin, 15
Atropine, cadaveric, 41
Autogenous disease, 128
Autotoxæmia, 128
puerperal, 152
Avian septicæmia, orrhotherapy in, 245

Bacillus botulinus, 48
bovis morbificans, 44
coli, development of, in the organs after death, 159
piscicidus agilis, 40
prodigiosus favoring the development of symptomatic anthrax, 174
Bacteria, action of, in the causation of disease, 3
anæmia theory of the action of, 5
causal relation of, to infectious diseases, 142
chemical theory of the action of, 6
dosage of, in relation to infection, 142, 296, 370
found in cases of ice-cream and cheese poisoning, 60
growth of, in culture media and in the living body, 294
in milk, 50

Bacteria, mechanical-interference theory of the action of, 5
of cholera, 325
of mumps, 559
of smallpox, 399
of vaccina, 399, 515
oxygen-consuming theory of the action of, 4
pathogenic, 25
peptonizing, in milk, 50
poisons elaborated by, see *Bacterial poisons*
proteid-consuming theory of the action of, 5
susceptibility to the invasion of, 166
toxicogenic, 25
water-borne, 293
Bacterial alkaloids, 10
Bacterial poisons, 3
classification of, 9
general effects of, 80
of anthrax, 81
of Asiatic cholera, 83
of diphtheria, 93
of glanders, 109
of hog cholera, 108
of malignant œdema, 110
of rabbit septicæmia, 110
of suppuration, 105
of tetanus, 89
of tuberculosis, 98
of typhoid fever, 96
Bacterial proteids, 21
Bacterial toxins, 23
Barben cholera, causation of, 40
Bartholin's glands, inflammation of, in mumps, 583
Bath, continuous, apparatus for, 490
warm, in the treatment of smallpox, 488
Bedsores complicating smallpox, 431
Betain, 16
Bilharzia hæmatobia, water-borne, 292
Blood, alteration of the, in hemorrhagic smallpox, 424
Blood-serum, see *Serum*
Boiling, purification of water by, 360
Book infection, 189
Botulinic acid, 47
Botulismus, 33, 46
Breasts, inflammation of the, in mumps, 583
Breath, leucomaïns in the, 124
probably free from microbes, 137
Bromatotoxismus, 26
Brouardel, P., on Vaccina, 499
Bryce's test of normal vaccina, 473
Butylamin, 12

Cadaverin, 13
in cholera cultures, 86
Calcium hydrate, purification of water by, 362
Calcutta, water-supply of, in relation to cholera, 342
Caproylamin, 12
Carnin, 121
Cell-nucleus, adenin obtained from the, 112
Charcot-Leyden crystals, composition of, 122
Chemotactic sensibility, 217
Chemotaxis, 210
influence of, on infection, 165
negative, 211, 218
positive, 211, 217, 218
Cheese poisoning, 57
Chickenpox and smallpox, non-identity of, 561
diagnosis of, from smallpox, 447
incubation period of, 374
infectious period of, 374
Cholera, Asiatic, agency of fairs, pilgrimages, and the like in the spread of, 349
bacteria of, 325
bacterial poison of, 83
epidemics of, showing the agency of water in the spread of the disease, 329
incubation period of, 384
infection difficult to trace in all cases of, 343
infectious period of, 384
orrhotherapy in, 254
protective influences against, in India, 349
route of, in the invasion of Europe, 350
spread of, by flies, 188, 304
water-borne, 324

Cholera, Asiatic, water-borne, definition of this phrase, 348
barben, causation of, 40
hog, see *Hog cholera*
infantum, ptomaïn found in the stools in, 18
reaction, 83
red, 84
blue, 84
vibrio, 325
poison of the, 83
Cholin, 15
Clavelization, 472
Clupea thirissa and C. venenosa, poisoning by, 37
Cocaine in the treatment of smallpox, 483
Coefficient, urotoxic, 127
Cold, effect of, in increasing susceptibility to infectious disease, 197
Collidin, 12
Colon bacillus, relation of, to the typhoid bacillus, 97
Comby, Jules, on Mumps, 553
Comma bacillus, 325
poison of the, 83
Conjunctivitis in smallpox, 431
Contagion, spread of disease by, 136
Contagious, see *Infectious*
Convalescence from infectious diseases, special susceptibility to smallpox during, 398
Copper poisoning, water-borne, 287
Cornea, lesions of the, in smallpox, 432
Corn poisoning, 76
Cornutin, 67
Cowpox and smallpox, non-identity of, 508
horsepox, and vaccina in man, relations of, 503
Creotoxicon, 44
Creotoxismus, 42
Crusokreatinin, 123
Cure, Bouchard's theory of, 179
Cystitis in smallpox, 437
Cytosin, 121

Deafness in mumps, 592
in smallpox, 434
Delirium in mumps, 589
in smallpox, 420, 437
treatment of, 489, 492
Dengue, incubation period of, 382
infectious period of, 382
Diarrhœa caused by milk poisoning, 53
complicating smallpox, 437
treatment of, 491
water-borne, 287, 358
Diethylamin, 11
Digestive organs, disorders of, caused by impure water, 287
Dihydrolutidin, 12
Dimethylamin, 11
Diphtheria, antitoxin of, 262
mode of action of, 265
bacillus of, rate of multiplication of, 367
bacterial poison of, 93
incubation period of, 377
infectious period of, 377
of the skin, 368
orrhotherapy in, 259
Disease, autogenous, 128
infectious, see *Infectious disease*
Dispora variolæ, 400
Distoma hepaticum, water-borne, 293
Dracunculus persarum, water-borne, 291
Dragon weaver, poisoning by the, 33
Drinking-water, dangers of impure, 283
essentials of pure, 359
Drug eruptions, diagnosis of, from smallpox, 447
Dysentery, water-borne, 357
Dyspepsia, water-borne, 357

Ears, affections of the, in mumps, 569, 592
in smallpox, 433
Ecthyma, vaccinal, 538
Ectogenous disease, relative immunity of the colored races to, 141
Eczema, solar, caused by the actinic rays, 476
vaccinal, 533
Endocarditis in mumps, 586
in smallpox, 435
malignant or ulcerative, diagnosis of, from smallpox, 452
Endogenous disease, relative immunity of the white races to, 141
England, cholera epidemics in, proving the water-borne nature of the disease, 329

Enteric fever, see *Typhoid fever*
Entozoa, water-borne, 290
Episarkin, 121
Ergot, poisoning by, 66
Ergotinic acid, 67
Ergotism, 66
  acute, 68
  chronic, 69
  gangrenous, 70
Ernst, Harold C., on Infection and Immunity, 133
Erysipelas complicating smallpox, 430
  diagnosis of, from smallpox, 449
  vaccinal, 534
Erythema, solar, caused by the actinic rays, 476
  vaccinal, 532
Ethylamin, 11
Ethylidenediamin, 13
Europe, introduction of smallpox into, 393
Expired air, leucomaïns in, 124
  probably free from microbes, 137
Eyes, affections of the, in mumps, 592
  in smallpox, 431

Fairs, agency of, in the spread of cholera, 349
Febris variolosa, 412
Fever, 185
  infectious, 182
  in mumps, 575
  in smallpox, 410, 427
    secondary, 428
  vaccinal, 517
Filaria sanguinis hominis, water-borne, 292
Filtration, purification of water by, 361
Fish, poisoning by, 33
  symptoms, 41
Floods, danger of, to the water-supply of cities, 299
Fœtus, acquired immunity of the, 223
  infection of the, 147
  smallpox of the, 397
Food, poisoning by, 26
  resulting from the conversion of cholin into neurin, 16
  vegetable, 66
  typhoid infection in, 303
Furunculosis complicating smallpox, 421, 431
  due to absorption of toxins from the intestinal canal, 167

Gadinin, 17
Galactotoxismus, 49
Genoa, cholera epidemic of 1884 in, showing the water-borne nature of the disease, 337
Gerontin, 121
Glanders, bacterial poison of, 109
  diagnosis of, from smallpox, 449
Glands, Bartholin's, inflammation of, in mumps, 583
  lymphatic, inflammation of, in mumps, 584
  salivary, swelling of, in mumps, 570
  thyroid, swelling of, in mumps, 584
  vulvar, inflammation of, in mumps, 583
Grease, relation of, to vaccina, 504
Grippe, see *Influenza*
Ground-water theory of typhoid fever prevalence, 314
Guanidin, methyl, 14, 110
Guanin, 116
Guinea-worm, water-borne, 291

Hæmatophilia, acute variolous, 424
Hæmaturia in mumps, 587
  in smallpox, 437
Hamburg, cholera epidemic of 1892 in, proving the water-borne nature of the disease, 334
Hart, Ernest, on Water-borne Diseases, 281
Headache, following exposure to typhus fever, 380
  in smallpox, 409
Heart, affections of the, in mumps, 586
  in smallpox, 435
  feebleness of the action of the, in cheese poisoning, 60
Herpes, diagnosis of, from smallpox, 449
  following vaccination, 533
Heteroxanthin, 119
Hexamethylenediamin, 14
Histon, 112
Hog cholera, bacterial poison of, 108

Hog cholera, orrhotherapy in, 243
Honey, poisonous, 39
Hornpox, 419, 423
Horsepox and smallpox, non-identity of, 508
cowpox, and vaccina in man, relations of, 503
spontaneous, 504
Hydrocollidin, 12
Hydrophobia, see *Rabies*
Hypoxanthin, 113

Ice-cream poisoning, toxicogenic germ in, 60
Ichthyotoxins, 40
Ichthyotoxismus, 33
Ihle's paste, 487
Immunity, 205
acquired, 207, 239
antitoxin theory of, 215, 220, 228
artificial, by means of the defensive proteids, 234
Bouchard's theory of, 179, 221
Charrin's theory of, 221
Chauveau's theory of, 222
conferred by one attack of smallpox, 398
defensive-proteids theory of, 215, 220, 228
destruction of, 208
diminution of, 166
due to phagocytes, 171
due to serum, characteristics of, 268
exhaustion theory of, 209
experimental, 207
hereditary transmission of, 279
humoral theory of, 213, 218
intrauterine acquisition of, 223
natural, 206
phagocytic theory of, 210, 216
production of a local lesion in, 176
retention theory of, 209
theories of, 209, 216, 273
vaccinal, 518
Impetigo, vaccinal, 538
Incubation and Infectiousness in Acute Specific Diseases, Duration of the Periods of, 367
smallpox, 373; chickenpox, 374; measles, 374; German measles, 375; scarlet fever, 376; diphtheria, 377; whooping-cough, 378; mumps, 379; typhus fever, 380; typhoid fever, 381; relapsing fever, 382; dengue, 382; influenza, 382; yellow fever, 383; Asiatic cholera, 384; bubonic plague, 384; malarial fever, 385; bibliographical references, 385
Incubation period of infectious diseases, 203, 367
Asiatic cholera, 384
bubonic plague, 384
chickenpox, 374
cholera, 384
definition of, 367
dengue, 382
diphtheria, 377
enteric fever, 381
German measles, 375
grippe, 382
influenza, 382
malaria, 385
measles, 374
mumps, 379, 568
parotitis, 379, 568
pertussis, 378
plague, 384
relapsing fever, 382
rötheln, 375
rubella, 375
rubeola, 374
scarlet fever, 376
smallpox, 373, 408
typhoid fever, 381
typhus fever, 380
vaccina, 516
varicella, 374
variola, 373
whooping-cough, 378
yellow fever, 383
India, antiquity of smallpox in, 390
origin of great cholera epidemics in, 339
Indol in cholera cultures, 83
Infection, 135
a chemical question, 146
Infection and Immunity, 135
infection, 135; chemotaxis, 165; predisposition to infectious disease, 166; insects as carriers of infection, 187; mixed infection, 190; late results of infection, 193; external pre-

disposing influences, 196; rôle of the nervous system, 200; periods of incubation and infectiousness, 203; prevention of infectious diseases, 204; *immunity*, 205; destruction of immunity, 208; theories of immunity, 209; *serum treatment*, 235; general properties of serum, 235; serum treatment in experimental diseases, 240; serum treatment in human diseases, 248; serum treatment in poisoning by vegetable toxalbumins and the venoms of serpents, 265; characteristics of the immunity due to serum, 268; the active element of the serum, 270; theory of the protective action of serum, 273; nature of the germicidal constituent of the blood serum, 277; the hereditary transmission of immunity, 279
Infection, bacterial products favoring the development of, 173
biotic agents of, 145
Bouchard's theory of, 179
causal relation of microorganisms to, 142
checked for a time by phagocytosis, 370
dosage of bacteria necessary for, 142, 296, 370
ectogenous, 140
endogenous, 140
external predisposing influences, 196
fever in, 182
fœtal, 147
germinative, 147
influence of anæsthetic substances upon, 169
of chemical substances upon, 169
of chemotaxis upon, 165
of digestion upon, 295
of dosage of bacteria upon, 142, 296, 370
of exposure of the animal to injurious influences upon, 167
of introduction of products secreted by the bacterium inoculated, 166
of microbian association upon, 167
of race upon, 140
Infection, influence of racial temperature upon, 181
of season upon, 146
of traumatism upon, 167
insects as carriers of, 187, 188, 303, 304, 355
intestinal, 155
intrauterine, 147
of smallpox, 148, 397, 520
of vaccina, 148, 520
late results of, 193
mixed, 190
modes of, 136
in smallpox, 400
obscurity of the subject, 301
of new-born infants, 155
part played by the local lesion in, 176
protective function of the spleen, 186
puerperal auto-, 152
rôle of the nervous system in, 200
spread of, 138
by books, 189
through the lungs, 159
toxic agents of, 145
water-borne, 289, 293
prevention of, 359
Infectious disease, bacterial production of, 3
definition of, 8
incubation periods of, 367
nature of, 135
poisons of the, 80
predisposition to, 166
prevention of, 204
Infectiousness, periods of, 203
Asiatic cholera, 384
bubonic plague, 385
chickenpox, 374
cholera, 384
dengue, 382
diphtheria, 377
German measles, 375
influenza, 383
measles, 375
mumps, 379, 566
parotitis, 379, 566
pertussis, 378
plague, 385
relapsing fever, 382
rubella, 375

Infectiousness, periods of, rubeola, 375
scarlet fever, 376
smallpox, 373, 406
typhoid fever, 381
typhus fever, 380
varicella, 374
variola, 373
whooping-cough, 378
yellow fever, 383
Inflammation, cause of, 143
Influenza, incubation period of, 382
infectious period of, 383
Insanity, rôle of bacteria in the production of, 200
Insects as carriers of infection, 187
in cholera, 188, 304
in malaria, 355
in typhoid fever, 303
Insomnia in smallpox, treatment of, 492
Intestinal tract, infection through the, 155
Iodism, mumps-like, 596
Isoamylamin, 12

Joint-disease in smallpox, 441

Kakké, alleged causation of, by eating of fish, 35
Keratitis in smallpox, 433
Knetkäse, poisonous properties of, 64
Kreotoxicon, 44
Kreotoxismus, 42

Larynx, lesions of the, in smallpox, 434
treatment of, 491
Lathyrism, 72
symptoms, 75
treatment, 76
Lead poisoning, predisposition to, 286
water-borne, 283
Leprosy, vaccinal, 473, 545
Leucocytes, eosinophilic, 216
mononuclear, 216
phagocytic, 210
polynuclear, 217
Leucocythæmia, adenin in the urine in, 112
hypoxanthin in the urine in, 114
xanthin in the urine in, 118
Leucomaïns, 110
Leucomaïns, kreatinin group, 122
relation of, to disease, 128
undetermined, 124
uric-acid group, 111
Leuconuclein, 112
Lime, purification of water by, 362
Liver, changes in the, in smallpox, 444
Liver fluke, water-borne, 293
Local lesion, part played by the, in infections, 176
Lumbago, diagnosis of, from smallpox, 445
Lumbricoid worms, water-borne, 290
Lungs, infection through the, 159
Lymph, vaccine, 471
active element of, 512
animal, 545
glycerinized, 549
Lymphatic ganglia, swelling of the, in mumps, 584
Lymphocytes, 216
Lysatin, 122
Lysatinin, 122

Macrophagocytes, 210
Maïdismus, 76
Malaria, air-borne, 352, 356
incubation period of, 385
mosquitoes as carriers of, 355
plasmodium of, life history of the, 354
soil-bred, 352
water-borne, 351
Malignant œdema, bacterial poison of, 110
Malleïn, 109
Mania, acute, in smallpox, 438
Mastitis in mumps, 583
Measles, diagnosis of, from smallpox, 446
incubation period of, 374
infectious period of, 375
Meat, poisoning by, 42
symptoms, 46
treatment, 49
transmission of disease by, 42
Mecca, cholera spread by the annual pilgrimage to, 350
Meningitis, diagnosis of, from smallpox, 450
in smallpox, 438

Metchnikoff's theory of phagocytosis, 210
Methylamin, 11
Methyl guanidin, 14, 110
Methylxanthin, 119
Microbes, see *Bacteria*
Microörganisms, see *Bacteria*
Microphagocytes, 210
Miliaria, vaccinal, 532
Milk, immunizing power of, 273
poisoning by, 49
treatment, 56
spread of typhoid infection in, 312, 322
Moore, John William, on Smallpox, 387
Morbilli, see *Measles*
Morrhuic acid, 18
Morrhuin, 15
Morvin, 109
Mosquito, agency of the, in the spread of malaria, 355
Mouth, lesions of the, in mumps, 573
in smallpox, 437
Mumps, 555
history, 555; geographical distribution and epidemics, 556; pathological anatomy, 558; bacteriology, 559; etiology, 563; symptoms, 568; course and duration, 577; extrasalivary localizations and complications, 578; prognosis, 593; diagnosis, 595; treatment, 598; bibliographical references, 602
Mumps, abortive forms, diagnosis of, 597
adenitis in, 584
age in relation to, 564
albuminuria in, 587
anasarca in, 587
bacteriology, 559
buccal mucous membrane in, 573
chronic forms of, 577
circulatory disturbances in, 586
complications, 584
contagion of, weak, 565
convalescence, 576
course, 577
deafness in, 592
delirium of, 589
diagnosis, 595
Mumps, diagnosis from adenitis, 595
from non-specific parotitis, 595
of abortive forms, 597
digestive disturbances in, 585
duration, 577
ear troubles in, 569, 592
epidemics of, 557
etiology, 563
extrasalivary localizations, 578
eye troubles in, 592
fever in, 575
genital localizations of, 578
geographical distribution of, 556
hæmaturia in, 587
heart troubles in, 586
history, 555
incubation period of, 379, 568
infectious period of, 379, 566
iodic, 596
invasion of, 568
localizations of, in other than the salivary glands, 578
lymphatic swelling in, 584
mastitis in, 583
nephritis complicating, 587
nervous complications of, 589
orchitis of, 559, 578, 594, 601
otalgia in, 569
ovaritis in, 583
paralysis following, 590
parotid swelling in, 570
pathological anatomy, 558
peritonitis in, 581
prognosis, 593
prophylaxis, 598
prostatitis in, 582
respiratory complications of, 586
rheumatism complicating, 586
salivary secretion in, 574
sex in relation to, 564
skin affections in, 588
sublingual swelling in, 573
submaxillary swelling in, 572
suppurative, 585
symptoms, 568
general, 575
synonyms, 555
testicular lesions of, 559, 578, 594, 601
thyroid swelling in, 584
treatment, 598

Mumps, treatment of grave and complicated cases, 601
of mild cases, 600
preventive, 598
universality of, 555
urethritis in, 582
vulval inflammation in, 583
Muræna helena, poisoning by, 35
Muscarin, 16
Muscle, leucomaïns in, 123
Mushrooms, poisonous, active principle of, 17
Mussels, poisoning by, 27
prophylaxis, 32
symptoms, 28
theory of the causation of, 30
treatment, 32
Mycophylaxins, 215
Mycosozins, 215
Mydalein, 19
Mydatoxins, 17
Mydin, 15
Myocarditis in smallpox, 435
Mytilotoxin, 17, 31
Mytilotoxismus, 27

Naples, cholera epidemic of 1884 in, showing the water-borne nature of the disease, 335
Nephritis in mumps, 587
in smallpox, 437
Nerves, section of, producing susceptibility to infectious diseases, 168
Nervous prostration in fevers, Graves' remedy for, 493
symptoms in mumps, 589
system, rôle of the, in infection, 200
Neuridin, 14
Neurin, 15
Neuritis, peripheral, in smallpox, 439
New-born infants, infection of, 155
Nuclein, adenin derived from, 111
Nucleohiston, 112

Œdema, malignant, bacterial poison of, 110
Orchitis in mumps, 559, 578
prognosis, 594
treatment, 601
in smallpox, 440
Orrhotherapy, 235
Orrhotherapy in anthrax, 242
in Asiatic cholera, 254
in avian septicæmia, 245
in diphtheria, 259
in experimental diseases, 240
in hog cholera, 243
in human disease, 248
in pneumonia, 250
in poisoning by serpent venom, 266
in poisoning by vegetable toxalbumins, 265
in rabies, 249
in septicæmia produced by the staphylococcus pyosepticus, 241
in streptococcus infection, 253
in symptomatic anthrax, 247
in tetanus, 255
in tuberculosis, 248
in typhoid fever, 249
milk as an agent in, 273
nature of the germicidal constituent of the blood serum, 277
specific nature of, 276
theory of the protective action of serum, 273
Otalgia in the invasion period of mumps, 569
Ovaritis in mumps, 583
in smallpox, 440
Oxyneurin, 16
Oxyuris vermicularis, water-borne, 291
Oysters, spread of disease by, 298, 304

Paralysis following mumps, 590
Paraplegia in smallpox, 438
Parasites, animal, water-borne, 290
Paraxanthin, 120
Parotid glands, swelling of, in iodism, 596
in mumps, 570
Parotiditis, parotis, or parotitis, see *Mumps*
Parvolin, 13
Pellagra, 76
symptoms, 78
treatment, 79
Pemphigus complicating vaccina, 533
diagnosis of, from smallpox, 450
Peptotoxin, 20
Pericarditis in mumps, 586
in smallpox, 435

Perichondritis laryngea variolosa, 434
Peritonitis in mumps, 581
in smallpox, 437
Pertussis, see *Whooping-cough*
Pettenkofer's ground-water theory, 314
Phagocytes, 271
fixed, 210
free, 210
immunity due to, 171
macro-, 210
micro-, 210
stimulation of, in explanation of orrhotherapy, 275
Phagocytosis, 210, 216
retardation of infection by, 370
Phlegmasia alba dolens in smallpox, 436
Phlegmons, vaccinal, 533
Phlogosin, 20, 105
attraction of leucocytes by, 170
Phylaxins, 215
Pilgrimages, agency of, in the spread of cholera, 349
Pitting of smallpox, 413, 416
prevention of, 475, 485
Plague, bubonic, incubation period of, 384
infectious period of, 385
Plasmodium of malaria, life history of the, 354
Pleurisy in smallpox, 435
Plotosus lineatus, poisoning by, 35
Plumbism, water-borne, 283
Pneumonia, orrhotherapy in, 250
septic, from meat poisoning, 47
Pock, diphtheritic, in smallpox, 442
of inoculated smallpox, 463
of smallpox, 441
reticulating and ballooning colliquation of the, in smallpox, 443
vaccinal, 517
Pock-marks, 413, 416
Poisoning, arsenic, water-borne, 287
cheese, 57
copper, water-borne, 287
corn, 76
ergot, 66
fish, 33
food, 26
through the conversion of cholin to neurin, 16
lead, water-borne, 283
Poisoning, meat, 42
milk, 49
mussel, 27
ptomaïn, diagnosis of, from smallpox, 447
water-borne, 287
sausage, 46
serpent-venom, orrhotherapy in, 266
shell-fish, 27
vegetable-food, 66
vegetable-toxalbumin, orrhotherapy in, 265
vetch, 72
zinc, water-borne, 287
Poisons, bacterial, see *Bacterial poisons*
Predisposition to infectious diseases, 166
increased by alcohol, 460
too great importance attached to, 140
Proteids, antitoxic, 232
attenuating, 231
bacterial, 21
cellular, 22
bactericidal, 229
defensive, 215, 220, 228
Propylamin, 12
Prostatitis in mumps, 582
Psoriasis following vaccination, 533
Ptomaïns, 9
poisoning by, diagnosis of, from smallpox, 447
water-borne, 287
Ptomaïns, Toxins, and Leucomaïns, 3
bacterial poisons, 3; ptomaïns, 9; bacterial proteids, 21; bacterial toxins, 23; food poisoning, 26; mussel poisoning, 27; fish poisoning, 33; meat poisoning, 42; milk poisoning, 49; cheese poisoning, 57; vegetable food poisoning, 66; poisons of the specific infectious diseases, 80; leucomaïns, 110; relation of leucomaïns to disease, 128
Ptomatins, 9
Ptomatropin, 41
Ptyalism, see *Salivation*
Puerperal autoinfection, 152
Pupil, dilatation of the, in cheese poisoning, 58
in fish poisoning, 41

Purpura variolosa, 424
bacteria not necessary to the occurrence of, 144
bacterial poison in, 105
feeble immunizing power of, 271
sterilized, toxic properties of, 108
Putrescin, 13
in cholera cultures, 84
Putrid poison in decomposed meat, 44
Pyæmia in smallpox, 441
Pyridin bases, 12, 13
Pyrotoxina bacterica, 183
Pyocyanin, 20

Rabbit septicæmia, bacterial poison of, 110
Rabies, orrhotherapy in, 249
Rachialgia in smallpox, 409, 438
Racial susceptibility to disease, 140
to smallpox, 397
temperature, influence of, upon the susceptibility to infectious diseases, 181
Rashes, medicinal, diagnosis of, from smallpox, 447
Red light in the management of smallpox, 461, 475
Relapsing fever, incubation period of, 382
infectious period of, 382
Respiration, bacteria probably absent from the expired air, 137
leucomaïns in the expired air, 124
Revaccination, 521
Rheumatism, acute, diagnosis of, from smallpox, 450
complicating mumps, 586
Romberg's symptom in ergotism, 69
Roseola variolosa, 410
Rötheln, see *German measles*
Rouget, see *Hog cholera*
Rubella, see *German measles*
Rubeola, see *Measles*

Saliva, leucomaïns in the, 128
secretion of, in mumps, 574
Salivary glands, swelling of the, in mumps, 570
Salivation in confluent smallpox, 419
in mumps, 575
Sapin, 14
Sarkin, 113
Sausage poisoning, 46
Scarlet fever, diagnosis of, from smallpox, 445
incubation period of, 376
infectious period of, 376
Scarus, poisoning by certain species of, 37
Sclerosis, disseminated spinal, in smallpox, 440
Scombridæ, poisoning by fish of the family of, 36
Scorpæna scrofa, poisoning by, 35
Season, influence of, upon infection, 146
relation of smallpox to, 394
Sea weaver, poisoning by the, 33
Sedimentation, purification of water by, 361
Sepsin, 45
Septicæmia, avian, orrhotherapy in, 245
in smallpox, 441
produced by the staphylococcus pyosepticus, orrhotherapy in, 241
vaccinal, 534
Serotherapy, see *Orrhotherapy*
Serpent venom, orrhotherapy in poisoning by, 266
Serum, active element of the, 270
antidiphtheritic, 262
antipneumonic, 261
antistreptococcic, 253
antitoxic power of, 238
antivenomous, 267
attenuating power of the, 237
bactericidal power of, 236
characteristics of the immunity due to, 268
coagulating power of, 240
general properties of, 235
globulicidal power of, 240
immunizing power of, 239
nature of the germicidal constituent of the, 277
specific action of, in orrhotherapy, 276
theory of the protective action of, 273
toxic power of, 240
treatment by, 235. See *Orrhotherapy*

Sewage farms, danger of, as regards the transportation of entozoa eggs and embryos, 291
Sewer gas, effects of, predisposing to infectious disease, 303
poisoning by, 288
Sheeppox, inoculation of, 462, 506
Shell-fish poisoning, 27
Siguatera, 33
Sitotoxismus, 66
Skin, affections of the, in mumps, 588
complicating smallpox, 430
Smallpox, 389
definition, 389; history, 390; etiology, 394; clinical history and symptomatology, 408; complications and sequelæ, 430; pathology, 441; diagnosis, 445; prognosis, 452; treatment, 457; bibliographical references, 496
Smallpox, abscesses complicating, 430
acne pustulosa complicating, 431
age as an etiological factor, 397
air-borne, 400
albuminuria in, 437
alcohol in the treatment of, 482
America invaded by, 393
and chickenpox, non-identity of, 561
and vaccina, mutually protective, 511
non-identity of, 508
bacteriology, 399
bathing in, 488
bedsores in, 431
black, 426
blood-changes in malignant, 424
bloody, 427
boils complicating, 431
classification of, 418
clinical history, 408
cocaine in the treatment of, 483
coherent, 422
colliquation of the pock in, 443
complications of, 430
treatment, 495
confluent, 414, 419
treatment, 481
conjunctivitis complicating, 431
corymbose, 422
crusts, 414, 443
Smallpox, cystitis in, 437
deafness in, 434
definition, 389
delirium in, 420, 437
treatment, 489, 492
desiccation of the eruption of, 414
desquamation, 415
diagnosis of, 445
from acne pustulosa, 450
from chickenpox, 447
from drug eruptions, 447
from endocarditis, 452
from erysipelas, 449
from glanders, 449
from herpes, 449
from lumbago, 445
from measles, 446
from meningitis, 450
from pemphigus, 450
from ptomaïn poisoning, 447
from rheumatism, 450
from scarlet fever, 445
from syphilis, 447
from typhus fever, 446
diarrhœa complicating, 437
treatment of, 491
diphtheritic pock, 442
discrete or distinct, 419
treatment, 480
ear complications of, 433
early literature of, 392
endocarditis in, 435
eruption of, 412
on the mucous membranes, 417, 420
erysipelas complicating, 430
etiology, 394
Europe invaded by, 393
eye complications of, 431
fever in, 427
of maturation or suppuration, 428
secondary, 428
fœtal, 148, 397, 520
glossitis in, 437
hæmaturia in, 437
heart troubles in, 435
hemorrhages in, 436
hemorrhagic, 424
treatment, 495
history, 390

Smallpox, hospitals for, dangerous to the neighborhood, 401
hyperpyrexia in, 428
immunity against, conferred by one attack of, 398
conferred by vaccination, 518
incubation period of, 408
duration, 373
infectious period of, 373, 406
inoculation, 462
in animals, 509
insomnia in, treatment of, 492
intrauterine infection, 148, 397, 520
invasion stage of, 409
iron in the treatment of, 484
joint-disease in, 441
laryngitis in, 434
treatment, 491
liver changes in, 444
macules, 413
malignant, 424
treatment, 495
mania in, 438
masterpock, 463
meningitis in, 438
mortality of, 452
before vaccination, 393, 501
of confluent, 421
reduced by vaccination, 393, 452, 455, 464, 501
myocarditis in, 435
nephritis in, 437
neuritis in, 439
orchitis in, 440
original home of, 390
ovaritis in, 440
papules, 413, 441
paraplegia in, 438
pathology, 441
pericarditis in, 435
peritonitis in, 437
petechiæ in the stage of invasion, 411
phlegmasia alba dolens in, 436
pitting, 413, 416, 441
prevention of, 475, 485
pleurisy in, 435
pocks of, 413, 416, 441
prognosis, 452
prophylaxis, 458
ptyalism in, 419
Smallpox, pulse in, 410
purpuric, 424
purpuric rashes in the stage of invasion, 411
pustules, 413, 441
of inoculation, 463
pyæmia in, 441
quinine in the treatment of, 484
rachialgia in, 438
racial susceptibility to, 397
rash, 412
of the initial stage, 410
post-eruptive, 418
red light in the management of, 461, 475
respiration in, 410
respiratory complications of, 434
revaccination in the prevention of, 521
salivation in confluent, 419
scabs, 414, 443
seasonal prevalence of, 394
semiconfluent, 422
septicæmia in, 441
sequelæ, 430
sex in relation to, 398
skin complications in, 430
spinal sclerosis in, 440
stages of, 408
staphylococcia and staphylostreptococcia in, 418
stomatitis in, 437
swelling of the hands and feet in, 431
symptoms, 408
synonyms, 389
temperature in, 410, 427
tracheobronchitis in, 435
treatment, 457
curative, 474
of confluent, 481
of discrete, 480
of hemorrhagic, 495
of malignant, 495
preventive, 458
umbilication of the pock, 413, 441, 443
vaccination, 463, 501
varieties, 423
vesicles, 413
vitality of the poison of, 407

Smallpox, without eruption, 412
Smith, Solomon C., on Water-borne Diseases, 281
Snake-bites, orrhotherapy in, 266
Soil, cholera contamination of the, in India, 340
malaria regarded as a disease of the, 352
typhoid contamination of the, 314
Sore-heels, relation of, to vaccina, 504
Sozins, 215
Spasmotoxin, 12
Spermin, 121
Sphacelinic acid, 67
Spinal cord, bacterial origin of diseases of the, 202
diseases of the, in smallpox, 440
Spleen, protective function of, against infection, 186
Splenic fever, see *Anthrax*
Staphylococcia and staphylostreptococcia in smallpox, 418
Starvation, effect of, in increasing susceptibility to infectious disease, 197
Stimulants, indications for, in the treatment of smallpox, 482
Stimulin, 275
Streptococcal infection, orrhotherapy in, 253
Streptococcus variolæ et vaccinæ, 399
Sublingual glands, swelling of the, in mumps, 573
Submaxillary glands, swelling of the, in mumps, 572
Sunburn caused by the action of the actinic rays, 476
Suppuration, bacterial poison of, 105
without bacteria, 144
Susceptibility to bacterial infection, 166
Susotoxin, 14
Synanceia brachio, poisoning by, 34
Syphilis, diagnosis of, from smallpox, 447
inoculation of, 543
intrauterine infection of, improbable, 150
vaccinal, 473, 539

Tænia, water-borne, 290
"Tea-kettle policy" in the prevention of water-borne diseases, 360
Temperature lowered, increasing the susceptibility to infectious disease, 197
racial, influence of, upon the susceptibility to infectious diseases, 181
Testicles, inflammation of the, see *Orchitis*
Testicular fluid, active principle of, 122
Tetanin, 19, 89
Tetanotoxin, 12, 89
Tetanus, analysis of the toxin of, 24
bacterial poison of, 89
orrhotherapy in, 255
Tetrodon, poisoning by, 36
Thalassophryne, poisoning by, 35
Theobromine, conversion of xanthin into, 119
Thyroid gland, swelling of, in mumps, 584
Toxalbumins, bacterial toxins incorrectly so called, 23
vegetable, orrhotherapy in poisoning by, 265
Toxins, 215
bacterial, 23
conversion of, into antitoxin by electricity, 107
in the urine, 196
of anthrax, 82
of Asiatic cholera, 83
of diphtheria, 93, 259
of glanders, 109
of hog cholera, 108
of malignant œdema, 110
of pneumonia, 250
of rabbit septicæmia, 110
of suppuration, 105
of tetanus, 89
of tuberculosis, 98
of typhoid fever, 96
Toxophylaxins, 215
Toxosozins, 215
Tracheobronchitis in smallpox, 435
Trachinus draco, poisoning by, 33
Traumatism, susceptibility to infection increased by, 167
Triethylamin, 11
Trimethylamin, 11
Trimethylenediamin, 13
Tubercle bacilli, poison of, 98

Tubercle bacilli, pyogenic action of dead, 105
Tuberculin, 98
A, 99
effects of, 103
O, 100
R, 100
Tuberculosis, bacterial poison of, 98
flesh of animals affected with, 43, 189
intrauterine infection of, improbable, 151
orrhotherapy in, 248
vaccinal, 545, 549
Typhoid bacilli, dates of the appearance of, in the urine and fæces, 302
relation of, to the colon bacilli, 97
saprophytic existence of, 312
Typhoid fever, air-borne, 303, 316
bacterial poison of, 96
earth-borne, 314
ground-water theory, 314
incubation period of, 381
infectious period of, 381
insects as carriers of, 303
manner of infection, 303
milk-borne, 312, 322
orrhotherapy in, 249
oyster-borne, 298, 304
soil pollution, 314
walking cases instrumental in spreading, 311
water-borne, 302
epidemics of, 318
in relation to the London water-supply, 296
Typhotoxin, 17
Typhus fever, diagnosis of, from smallpox, 446
headache after exposure to, 580
incubation period of, 380
infectious period of, 380
Tyrotoxicon or tyrotoxin, 19, 57
in milk, 54
Tyrotoxismus, 57

Umbilication of the pock in smallpox, 441, 443
Urethritis in mumps, 582
Urine, leucomaïns in, 125
toxicity of the, 125
Urine, toxity of the, diminished during the febrile stage of acute infectious diseases, 370
toxins in the, 196
Urotoxic coefficient, 127
Urotoxy, 125

Vaccina, 501
discovery of vaccination, 501; relations of cowpox, horsepox, and vaccina in man, 503; non-identity of variola and vaccina, 508; the active elements of vaccine virus, 512; the normal vaccinal eruption, 515; vaccinal receptivity, 518; vaccinal immunity, 518; anomalies in the vaccine eruption, 527; coincident eruptions, 532; secondary infections, 533; animal vaccine, 545; indications and contraindications of vaccination, 549; methods of vaccination, 550; bibliographical references, 551
Vaccina, 464, 472, 501
active element of the virus of, 512
and smallpox, mutually protective, 511
non-identity of, 508
animal, 545
anomalies in the eruption of, 527
bacteria in, 399, 515
Bryce's test, 473
cicatrization stage of, 516
coincident eruptions, 532
complications of, 532
cowpox, and horsepox, relations of, 503
desiccation stage of, 516
eruption of, 516
anomalies in the, 527
erysipelas complicating, 534
false, 528
fever of, 517
gangrenous, 534
generalized, 530
hemorrhagic, 533
horsepox, and cowpox, relations of, 503
immunity against smallpox afforded by, 518
duration of, 520

Vaccina, incubation period of, 516
intrauterine transmission of, uncertain, 148, 520
modified, 528
secondary infections, 533
secretion stage of, 516
septicæmia complicating, 534
susceptibility to, 518
symptoms, 473, 515
ulcerative, 538
without eruption, 529
Vaccination, 463, 501
accidents of, 532
animal, 546
contraindications of, 549
discovery of, 464, 501
glycerinized pulp, 549
immunity against smallpox conferred by, 518
indications of, 549
influence of, upon the mortality from smallpox, 393, 452, 455, 464, 501
methods of, 470, 550
mortality from smallpox, prior to the introduction of, 393, 501
prevention of smallpox by, 464, 518
repeated, 521
rules for, 470, 550
scar, 517
Vaccine, see *Lymph, vaccine*
Vaccinoid, 528
Vaccino-leprosy, 473, 545
Vaccino-syphilis, 473, 539
Vaccino-tuberculosis, 545, 549
Vanilla, alleged poisoning by, 65
Vanillin, artificial, contaminated with bichromate of potassium, 65
Varicella, see *Chickenpox*
Variola benigna, 389, 423
confluens, 419
cornea, 419, 423
corymbosa, 422
cruenta, 427
crystallina, 419
discreta vel distincta, 419
dysenterica, 437
hæmorrhagica, 424
pustulosa, 426
maligna, 424
nigra, 426
Variola ovina, 462, 463
purpurica, 424
semiconfluens, 422
sine exanthemate, or sine variolis, 412, 423
vaccina, see *Vaccina*
verrucosa, 419, 423
see also *Smallpox*
Varioloid, 423
definition of, 389
Vaughan, Victor C., on Ptomaïns, Toxins, and Leucomaïns, 1
Vegetable food poisoning, 66
Venom, serpent, orrhotherapy in poisoning by, 266
Vetch poisoning, 72
Virus, vaccine, see *Lymph, vaccine*
Vulva, inflammation of the, in mumps, 583

Wartpox, 419, 423
Water-borne Diseases, 283
introduction, 283; diseases caused by non-living matter, 283; plumbism, 283; poisoning by zinc, copper, or arsenic, 287; dyspepsia, diarrhœa, and ptomaïn poisoning, 287; diseases caused by living organisms, 289; the entozoa, 290; bacteria, 293; typhoid fever, 302; cholera, 324; malaria, 351; dysentery, diarrhœa, and yellow fever, 357; preventive measures, 359; conclusions, 363; bibliography, 364
Water, boiling as a means of purifying, 360
calcium hydrate as a means of purifying, 362
filtration as a means of purifying, 361
plumbo-solvent action of, 284
purification of, 360
sedimentation as a means of purifying, 361
sterilization of, 360
subsoil, drawn into supply pipes, 316, 319
Water-supply, dangers of a contaminated, 283
essentials of a pure, 359

Water-supply, fouled by in-sucking by leaky pipes, 316, 319
Whooping-cough, incubation period of, 378
infectious period of, 378
Williams, Dawson, on The Duration of the Periods of Incubation and Infectiousness in Acute Specific Diseases, 365
Worms, intestinal, water-borne, 290

Xanthin, 117
Xanthokreatinin, 123

Yellow fever, incubation period of, 383
infectious period of, 383
water- borne, 359

Zinc poisoning, water-borne, 287
Zymotic diseases, see *Infectious diseases*

RC41 St3
Stedman 13